Fractionation and Dose Rate in Radiotherapy

An Experimental and Clinical Study of Cumulative Radiation Effect

By

Ingela Turesson

Göteborg 1978

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From the Radiation Physics Department (Director: Prof. H. Sköldborn) and the Radiation Therapy Department (Director: Prof. G. Notter), Sahlgrenska sjukhuset, S-413 45 Göteborg, Sweden

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AKADEMISK AVHANDLING

som med vederbörligt tillstånd av Medicinska Fakulteten vid Göteborgs universitet för vinnande av medicine doktorsexamen offentligen kommer att försvaras i föreläsningssalen, Konung Gustaf V:s Jubileumsklinik, Sahlgrenska sjukhuset, torsdagen den 12 januari 1978, kl 9 f.m.

Av

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FK, MK

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This thesis is mainly based on the following Papers, referred to in the text by their Roman numerals.

I Turesson Ingela and Notter Gustaf: Skin reactions after different fractionation schedules giving the same cumulative radiation effect.
Acta Radiol. Ther. Phys. Biol. 14: 475-484, 1975.

II Turesson Ingela and Notter Gustaf: Skin reaction as a biological parameter for control of different dose schedules and gap correction.
Acta Radiol. Ther. Phys. Biol. 15: 162-176, 1976.

III Turesson Ingela and Notter Gustaf: Control of dose administered once a week and three times a day according to schedules calculated by the CRE formula, using skin reaction as a biological parameter.
Radiology 120: 399-404, 1976.

IV Notter Gustaf and Turesson Ingela: Prospective studies with the CRE formula of prolonged fractionation schedules.
Radiology 121: 709-715, 1976.

V Turesson Ingela and Notter Gustaf: The response of pig skin to single and fractionated high dose-rate and continuous low dose-rate ^{137}Cs-irradiation.
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INTRODUCTION

The first establishment of a mammalian cell survival curve in vitro by Puck and Marcus in 1956 paved the way for a period of intensive development in the field of radiobiology. This approach made it possible to detect and quantitate basic radiobiological mechanisms such as

- inherent cellular radiosensitivity
- variation of radiosensitivity during the cell cycle
- irradiation-induced mitotic delay and cell cycle synchrony
- repair of radiation injury
- the oxygen effect
- the effect of linear energy transfer, LET

The possibilities of using these modern concepts of radiobiology to describe and predict the results of radiation therapy attracted considerable interest. Recently, interest has also been focused on the use of radiobiological data to improve radiotherapy. Prediction of the response of different tissues to irradiation is, however, further complicated by the influence of cell population kinetics, which is an even more recent subject of study.

In spite of all the experimental results available, no distinct differences in radiation response between normal and malignant cells and tissues can be established as a firm basis for improved clinical radiotherapy. Every radiotherapist is aware that injury to normal tissues may occur at dose levels required for destruction of cancer cell populations, and he has to accept a certain degree of risk for complications in order to cure the patient. The problem is the small margin in dose between adequate tumour control and an acceptable level of complications, and how to increase the radiation effect on tumours without increasing the morbidity. One approach to this problem is to establish optimal fractionation-time-dose distributions.

Increased knowledge of the influence of fraction size and frequency is also required when conventional dose schedules have to be altered for optimal combination of

radiotherapy with hyperbaric oxygen, radiosensitizers and chemotherapy.

The capacity of human cancer and normal cells for repair of sublethal radiation injury varies from tissue to tissue. As a generalization, the recovery potential seems to be greater in normal cells than in cancer cells (Denekamp and Harris 1976, Phillips 1972) which favours the differential survival of the former in fractionated radiotherapy. The problem of choosing optimal size and frequency of the fractional increments is also influenced by the cell kinetics of the tumour and the surrounding normal cells, which changes continuously during irradiation.

Recent experimental findings have stimulated interest in model-building for predicting optimal dose schedules. The models have become increasingly sophisticated with the increasing availability of computers. However, the usefulness of these models is so far limited by lack of information concerning the individual tumours and even for the critical normal tissues.

In clinical practice, therefore, one is still restricted to simple models as a guide for defining iso-effect relationships for different fractionation and dose-rate regimes. It is this fact, that has made the Ellis´ NSD- (Nominal Standard Dose) formula (1967) so popular during the last few years. This formula was the first attempt to separate and use the fractionation and the time factor in relating dose to the biological effect in radiotherapy, thereby implying an important extension of the iso-effect concept of Strandqvist (1944).

The formula is:

$$NSD = D \cdot N_{tol}^{-0.24} \cdot T^{-0.11}$$

where NSD, the Nominal Standard Dose, expresses the tolerance of normal connective tissue, D is the total dose [x)], N_{tol} (the suffix refers to the number of fractions needed to attain normal tissue tolerance) is the total number of fractions and T the overall treatment time in days. The NSD-formula has been described in several papers (Ellis 1968, 1969, 1971, 1974).

[x)] dose means absorbed dose throughout this presentation

Limitations of the NSD-formula

Ellis pointed out that the formula applies for:

- late effects on normal connective tissue
- a fraction number between 4 and 30
- a sufficiently long interval between fractions to allow for full repair of sublethal damage
- an overall treatment time between 4 and 100 days.

The NSD-formula has focused much attention on the importance of calculating iso-effect doses in radiotherapy and has sometimes met with considerable scepticism from many points of view. For example, it has been stated that the formula is based on extrapolation of too few and uncertain clinical data concerning skin, and the effect on skin may not be relevant to other tissues. Doubts have also been expressed about the importance and validity of rectilinear (in log-log scale) iso-effect curves. However, criticism of the formula often refers to clinical situations or experimental conditions for which the formula was not defined. Application of this model in retrospective studies may also result in uncertain conclusions. Furthermore, the formula has often been used in a mathematically incorrect way (Orton and Ellis 1973). So far, to my knowledge, no prospective clinical study of the validity of the NSD-formula has been published concerning late effects on normal connective tissue, for which the formula was really defined.

Generalization of the NSD-formula

The NSD-formula is applicable only at the tolerance level, defined as an acceptable degree of risk for complications. A new concept, partial tolerance (PT), was introduced for representing sub-tolerance levels (Winston et al 1969), where

$$PT = \frac{N}{N_{tol}} \cdot NSD$$

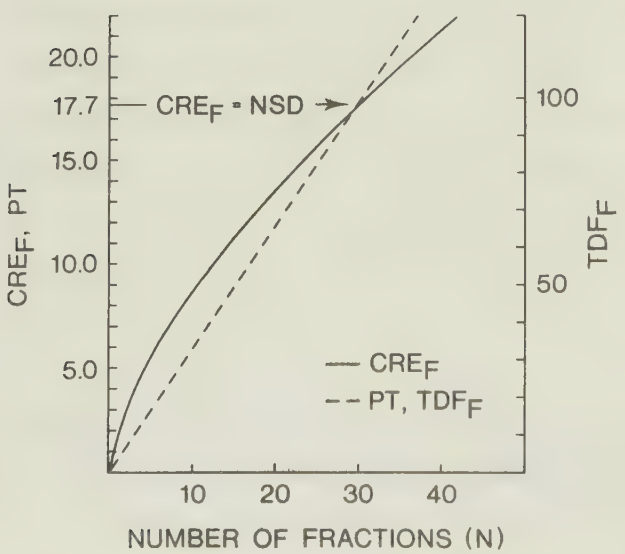
N is the number of fractions delivered, N_{tol} is the number of fractions required to reach the tolerance level using the same fractionation schedule, and NSD as above (always constant for a particular treatment).

The definition of partial tolerance (PT) in this way was developed for mathematical convenience only as the numerical values of partial tolerances are linearly additive. However, in order to use the PT concept it is necessary to know the value of NSD, which is considered to be constant for a given type of normal tissue and a given volume, but may vary between different centres owing to variation in criteria of tolerance.

This complication was overcome in the CRE_F- (Cumulative Radiation Effect) formula [x] presented by Kirk and his colleagues (1971) which is merely a generalization of the NSD-formula written in a somewhat different way:

$$CRE_F = \left(\frac{T}{N}\right)^{-0.11} \cdot d \cdot N^{0.65}$$

where d is the dose per fraction, N the number of fractions delivered and T the overall treatment time in days for N fractions (including the first and last day of treatment).



N	PT	CRE_F	TDF_F
20	11.8	13.6	66
30	17.7	17.7	99
35	20.7	19.6	115

Figure 1. Partial tolerance (PT), cumulative radiation effect (CRE_F) and time dose fractionation (TDF_F) factors as a function of the number of fractions (N) for 5 x 2.0 Gy per week and numerical values of PT, CRE_F and TDF_F for N = 20, 30 and 35.

x) The index F or C are used to separate the formulae for fractionated high dose-rate and continuous low dose-rate irradiation, respectively.

Unlike the NSD-formula, the CRE_F-formula is also defined for subtolerance levels. The CRE_F and NSD values are therefore only numerically comparable at the limit of normal connective tissue tolerance. This difference between the NSD – PT-formula and the CRE_F-formula is illustrated in Figure 1, in which the two different formulae are applied to the conventional treatment schedule: 30 fractions of 2.0 Gy within 6 weeks corresponding to a NSD and CRE_F value of 17.7. It will be seen that the radiation effect per fraction declines successively during the period of treatment, according to the CRE_F-model, but is constant in calculation of the PT. The two models are therefore not comparable at subtolerance level and above the tolerance level, which must be defined when using the concept of partial tolerance.

Another way to circumvent the problems involved in using the NSD-PT-model was presented by Orton (1973), who defined the time-dose and fractionation (TDF) factors. The TDF_F is related to PT by

$$PT = (NSD \cdot 100)^{-0.538} \cdot TDF_F \cdot 10^3$$

and TDF_F is defined as:

$$TDF_F = N \cdot (d \cdot 100)^{1.538} \cdot \left(\frac{T}{N}\right)^{-0.169} \cdot 10^{-3}$$

where N is the number of fractions delivered, d the dose per fraction in Gy and T the overall treatment time in days for N fractions. There is a small discrepancy in the definition of T between the NSD, TDF_F and CRE_F-models, as reviewed by Goitein (1976).

TDF_F is also plotted against the number of fractions for 5 x 2.0 Gy/week in Figure 1. The advantage of TDF_Fs is that they are linearly additive, like PTs, but not dependent upon any specific NSD value. In conclusion, all of these formulae (PT, CRE_F and TDF_F) result in identical dose levels in comparisons of different fractionation schedules. They are merely different ways of applying the NSD concept.

Models for continuous low dose-rate irradiation techniques

The importance of the time-dose distribution in interstitial, intracavitary and surface mould techniques has been established in iso-effect curves relating total dose to treatment time or dose rate by Mitchell (1960), Ellis (1970) and Paterson (1963) using clinical data. Ellis (1970) presented a table, based on the data from Green, for correction of the total dose with varying treatment times and included this later (Ellis and Sorensen 1974) in the NSD-model for calculation of the biological effect of combined fractionated high dose-rate and low dose-rate treatment in cancer of the cervix uteri.

Kirk et al (1972) developed a general formula based on the data reported by Ellis and Paterson for calculating CRE for continuous low dose-rate irradiation with constant dose rate throughout the period of treatment. The formula can be written in two forms:

$$CRE_C = k \cdot D \cdot T^{-0.29} \quad \text{or} \quad CRE_C = k \cdot r \cdot T^{0.71}$$

where D is the total dose delivered, T the total irradiation time in days and r the dose rate in dose per day. k is a normalizing constant to ensure equivalent radiobiological effects on normal tissue for the same value of CRE given either with fractionated high dose-rate or continuous low dose-rate irradiation. A value of k of 0.80 was proposed by Kirk et al (1975, 1977).

Orton (1974) also developed, by using all three clinical data sets mentioned above, a corresponding relationship for calculating TDF for continuous irradiation with constant dose rate throughout the period of treatment:

$$TDF_C = k \cdot (r \cdot 100)^{1.35} \cdot T \cdot 10^{-3}$$

where r, T and k have the same significance as in the CRE_C-model. k was found to be 1.57. The TDF_C-formula written above is defined for the absorbed dose expressed in Gy.

Liversage (1969) has presented a model to solve the problem of defining radiobiologically equivalent dosage regimes when converting the radium technique with continuous low dose-rate irradiation to the afterloading technique with fractionated high dose-rate irradiation. This formula for equating protracted and acute radiation regimes enables the dose necessary to produce a given effect using low dose-rate continuous irradiation to be converted to an approximately equivalent multi-fraction dose at high dose rate by relating the number of fractions, N, to the continuous irradiation time of t hours. For t greater than 12 hours N is approximately equal to t/4. If all fractions are given within t hours the total dose should be the same with both techniques. If the treatment time is prolonged an average dose increment per day was proposed to compensate for repopulation, which varies from tissue to tissue.

Unit for the biological effect

In using the models described for calculation of the biological effect of different treatment schedules, Papers I to V, the proposed units in these models were excluded, because the formulae are only used to describe the radiobiological effect in relative and not in absolute terms.

Development of other models

Some other promising ways of establishing fractionation models will be mentioned shortly. Mathematical formulae similar to that of Ellis with tissue-specific exponents for the fraction and time factors have been established from animal experiments (Wara et al 1973). Another approach which has been applied is that of using cell survival-curve data. Cohen (1971) has presented a two-component model including a growth function and a volume correction with numerical values of the parameters involved computed from clinical data for different normal tissues. Recently, Douglas and Fowler (1976) presented the "F_e concept" based on mouse skin experiments. F_e is the reciprocal of total dose and was found to be a linear function of dose per fraction over a wide range of fraction sizes.

Aim of the present investigation

The present series of investigations were designed to study the reliability of the CRE system for predicting equivalent biological effects on normal tissue after different dose-fractionation-time distributions in radiation therapy. In a clinical study the validity of the CRE_F (or NSD)-formula was determined for skin reactions to postoperative irradiation of breast cancer patients for:

I dose per fraction between 7.3 and 1.0 Gy, correlated to:
- a number of fractions between 4 and 50, and
- daily compared to once-a-week, twice-a-week and three-times-a-day irradiation within a fixed overall treatment time

II split course therapy with a gap of 3 weeks, and very prolonged treatment times, over 90 days.

In an experimental study the effect on pig skin of single and multifraction doses of irradiation applied at high dose rate (1.48 Gy/min) were compared with the effect of continuous irradiation at low dose rate (1.20 Gy/h). Dose-effect curves were established for these different irradiation regimes for determination of:

I the relative biological effectiveness (RBE) between single doses applied at high and low dose rate, and

II the correspondence of the CRE_F and CRE_C-formulae, i.e. the normalization constant, k.

It is well known that the tolerance of normal tissues is commonly the limiting factor in local tumour control with radiation therapy. However, optimal application of radiotherapy is still limited by lack of knowledge concerning the relationships between normal tissue complications (acute as well as late) and dose, and how different factors like fraction size, treatment time and dose rate modify these relationships. The correlation between acute and late reactions is not fully understood. In

some time-dose schedules, the severity of acute and late reactions is in parallel, but this is not always the case. Extreme fractionation schedules with short or very protracted treatment time, and schedules with very small or large fraction size, may influence acute and late responses differently.

As some clinical data have shown, (Morrison 1975, Stewart and Jackson 1975), there is a steep relationship between radiation dose and local tumour control rate. There is therefore a real need for better knowledge of the factors influencing normal tissue tolerance and for models which can predict equivalent total doses for a constant risk of complications with different irradiation techniques. Tumour recurrences because of a too low tumour dose, owing to an unjustified fear of normal tissue damage, can thereby be avoided.

This thesis deals with the application of the CRE system to these problems.

THE VALIDITY OF THE CRE_F-FORMULA FOR ACUTE SKIN REACTION IN MAN

The validity of the CRE_F-formula for predicting the dose levels required for equivalent acute skin reactions with varying fractionation schedules has been determined in 5 clinical investigations. Table I lists in chronological orders the different series, called CRE I to CRE V, with fractionation schedule, number of patients and length of follow-up.

Table 1. Dose schedules compared on bilateral parasternal fields (equivalent to ^{60}Co-radiation). xx)

SERIES	DOSE SCHEDULE	N (fract.)	T (days)	CRE_F	NO. of patients	FOLLOW-UP (months)	PAPER
CRE I	5 x 2.25 Gy/week	21	29	15.8	13	60	I
	2 x 4.30 "	9	29	15.8			
CRE II	5 x 2.43 Gy/week	18	24	15.4	14	4	II
	5 x 2.43 " (10 x 2.43 Gy, Gap for 3 weeks, 9.5 x 2.43 Gy)	19.5	47	15.4			
CRE III	5 x 2.56 Gy/week	16	22	15.1	10	3	II
	5 x 2.43 "	16	22	14.3			
CRE IV	5 x 2.54 Gy/week	16	22	14.9	27	36	III
	1 x 7.29 "	4	22	14.9			
CRE V	1 x 2.45 Gy/day ┐	17	23	15.0	11	34	III
	3 x 1.08 " ┘ 5 times a week ┘	50	23	15.0 (16.0) x)			

x) See paper III

PATIENTS AND METHODS

In the series CRE I to V patients operated upon for breast carcinoma were irradiated on two bilateral parasternal fields of 5 x 12 cm^2 with different dose schedules. The first-mentioned schedule in Table 1 for each series was always applied to the right field. The following radiation qualities were used:

xx) Rounding errors have resulted in small discrepancies between the CRE_F values in this Table and those presented in Paper I to III.

CRE I : Electrons, 13 MeV, dose rate about 0.6 Gy/min at the peak of absorbed dose.

CRE II to V: 200 kV X-rays, HVL 1.2 mm Cu, dose rate 0.74 Gy/min at the surface (peak of absorbed dose).

In connection with each radiation treatment thermoluminescent dosemeter (TLD) determinations were performed according to a technique described by Lindskoug (1975), see Figure 2. The TLD measurements at each session were regarded as a control of the relative dose difference between the two fields for each patient and between all the patients. If necessary, the dose to the last fraction was corrected according to the TLD determinations in order to achieve the required dose. The uncertainty in dose per fraction checked by TL-Dosimetry was presented in detail in Paper I to III.

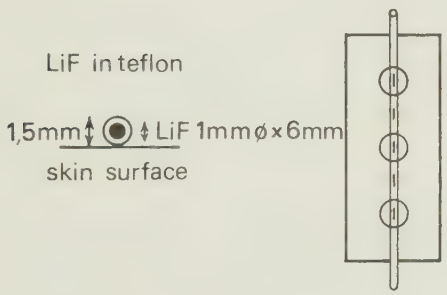


Figure 2.
Skin dose measurements with LiF in teflon probes. The upper, middle and lower dosemeters were always placed within the regions of the reflectance spectrophotometer measurements of erythema and pigmentation.

The absorbed dose per fraction quoted in Table 1 refers to the skin dose measured to 86 % of the peak absorbed dose for electrons and by using a f-factor of 0.0092 Gy/R for X-rays. RBE corrections of 1.00 and 1.17 for electrons and 200 kV X-rays, respectively, were applied for calculation of ^{60}Co-radiation-equivalent dose levels.

The final CRE_F values presented in the results were corrected according to the TLD determinations. In series CRE I the CRE_F calculations were based on the measured skin dose. In CRE II to V the CRE_F values for each series were normalized to the dose to the centre of the right field, assumed to be 100 %.

The biological effect of irradiation was determined by measuring the skin erythema and pigmentation, by means of reflectance spectrophotometry. An area of approximately 2.5 cm^2 was illuminated with light of wavelengths 578 nm and wavelengths above 660 nm. The amount of reflected light, modified by oxyhaemoglobin and melanin absorption, was read in scale divisions. Figure 3 shows the transmission characteristics of an interference filter with T_{max} at 578 nm and of a cut-off gelatin filter (Chu and coll. 1960, Nias 1963).

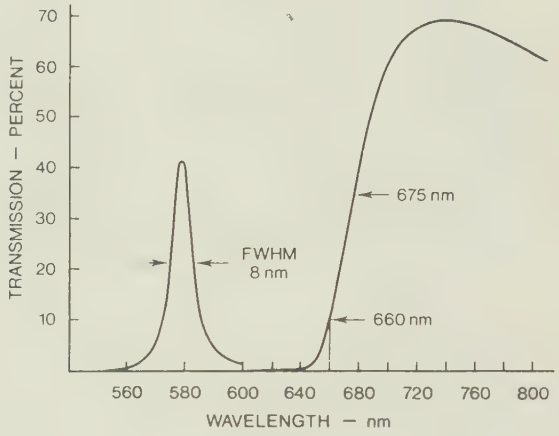


Figure 3.
Transmission characteristics of an interference filter, used for erythema measurements, and of a gelatin filter used for pigmentation measurements.

Measurements were performed twice weekly, commencing before the first treatment at 2 or 3 points per field. This was necessary to achieve adequate results, because erythema is generally more pronounced above the second intercostal space than below it, due to differences in the sympathetic tone (Adams-Ray 1952, Notter and coll. 1965). The precision of the individual reflectance measurement has been discussed in Paper I. The patients were also photographed at least once a week.

In the series CRE III we investigated whether a prescribed dose difference of 5 per cent caused any measurable difference in erythema and pigmentation, to obtain knowledge of the radiation sensitivity of skin and the accuracy of the spectrophotometry technique. The final difference in dose was 6 to 7 per cent, according to the TLD determinations, and in CRE_F 5 to 7 per cent. The result of this series indicated that by reflectance spectrophotometry the effect of such a dose difference could be measured significantly ($p < 0.05$) for skin erythema but not for pigmentation.

Fractionation schedules. In the series CRE I, IV and V daily irradiation five times a week was compared with irradiation twice a week, once a week and 3 times a day. The number of fractions, and thereby the dose per fraction, was varied, the treatment time being fixed in each series. The number of fractions varied between 4 and 50 and the dose per fraction between 1.08 and 7.29 Gy.

The series CRE V was performed to check the relevance of the CRE_F-formula for a dose schedule in which the fractions were repeated 3 times a day at 4-hour intervals. When calculating the CRE_F the irregular time interval between fractions in this schedule was taken into account, as outlined in Figure 4 and presented in the appendix to Paper III.

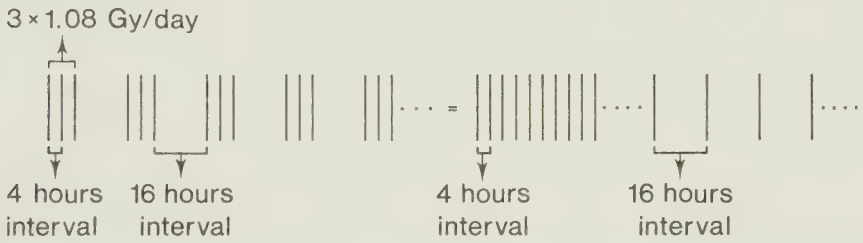


Figure 4. Outline of the fractionation schedule in the series CRE V and the permutation technique used to calculate the CRE_F for schedules involving 3 fractions a day.

This method of calculation was supported by the result of the series CRE V, which showed that this more complicated calculation, giving a CRE_F-value of 16.0, agreed much better with the observed early skin reaction than the CRE_F-value of 15.0 found by straightforward application of the CRE_F-formula (see Table 1).

In the series CRE II treatment schedules with and without a gap in the course of treatment were compared. The same dose per fraction was used throughout both courses and the decline in the effect during a 3-week gap was compensated for by increasing the number of fractions. This additional number of fractions was calculated from the Ellis´ correction applied to the CRE_F-formula, as described in Paper II, in which the correction proposed by Kirk (1975) is also discussed.

The early skin reaction for treatment courses prolonged over more than 90 days was described in Paper IV. The method and results of this study will only be given in summarized form in the discussion of this chapter.

RESULTS

The reflectance determinations of erythema and pigmentation for each patient were analysed separately in the upper, middle and lower parasternal region. At each point all measurements during and after the treatment courses were normalized to the pre-irradiation value at that point. The maximum skin reactions and the times for maximum involvement with corresponding CRE_F-values, corrected according to the TLD determinations, are presented in Tables 2 to 6. The originally published CRE_F-values for CRE II and III have been reduced in Table 3 and 4 for consistency according to revision of the f-factor from 0.0094 to 0.0092 Gy/R (Attix and Tochilin 1969, ICRU Rep 23, 1973), which did not influence the conclusions in these papers, however.

There was no significant difference ($p < 0.05$) in the maximum early skin reaction measured after the fractionation schedules compared in CRE I, II and IV (except for pigmentation in the upper region in CRE II). Neither were differences in erythema and pigmentation detectable visually. The results in CRE III were already mentioned on page 16.

In the CRE V the field treated 3 times a day received a 6 to 8 per cent higher CRE_F than the contralateral field (discussed in Paper III) which also resulted in a significantly more pronounced skin erythema and pigmentation ($p < 0.05$). This measureable difference in erythema was also obvious to the naked eye.

At the CRE_F levels used in these investigations all patients developed a dry erythema bordering on an exudative reaction when the CRE_F was close to 16.0. The maximum skin reactions developed 8 to 14 days after the end of radiation therapy. In the lower parasternal region, the skin reactions were generally less pronounced and became maximal a couple of days later than in the upper and middle region,

(Table 2 to 6). According to the reflectance determinations, erythema and pigmentation developed concomitantly and largely in parallel. Visually, this cannot be observed because the marked early erythema obscures the pigmentation, which does not become evident until the acute erythema has diminished.

The results demonstrate the possibility of correct iso-effect calculation with the CRE_F-formula for different types of fractionation in radiotherapy. By using reflectance spectrophotometry it was possible to verify a difference in early radiation effect on the skin caused by a dosage difference of 6 to 7 per cent (according to the findings in CRE III). We therefore consider that reflectance spectrophotometry is a useful technique for quantification of moderate skin reactions. The high accuracy achieved is mainly due to precise irradiation of identical and congruent areas with each patient as her own control. Thus, biological as well as physical variations can be reduced to a minimum.

In conclusion, for early skin reactions, we found that the reliability of the CRE_F-formula for prospective calculation of biologically equivalent radiation doses for the fractionation schedules investigated, CRE I, II, IV and V, was better than 7 per cent. It should be pointed out that the findings in CRE I, IV and V mainly concern the validity of the model for predicting the influence of varying number of fractions and fraction size, as the overall time was fixed in each series.

Table 2. Series CRE I. Cumulative radiation effect, and corresponding mean values of spectrophotometric measurements in the upper and lower parasternal regions (95 % confidence), and time for maximum skin reactions (mean and 95 % confidence)
Right field: 5 x 2.25 Gy/week, totally 47.25 Gy in 29 days (measurement points 1 and 3)
Left field : 2 x 4.30 Gy/week, totally 38.70 Gy in 29 days (measurement points 2 and 4)

		MEASUREMENT POINT			
		1 (upper region)	2	3 (lower region)	4
CRE_F		15.70 ± 35	15.70 ± 35	15.95 ± 30	15.90 ± 30
Maximum skin reaction (% of pre-irradiation value)	eryth.	59.4 ± 4.7	57.8 ± 3.7	51.8 ± 4.6	51.1 ± 3.9
	pigment.	16.7 ± 3.0	16.0 ± 3.8	12.9 ± 3.6	12.7 ± 3.2
Days after start of irradiation for maximum skin reaction	eryth.	40 ± 2	40 ± 2	43 ± 3	42 ± 3
	pigment.	41 ± 2	40 ± 2	44 ± 3	44 ± 3

Table 3. Series CRE II. Cumulative radiation effect, and corresponding mean value of spectrophotometric measurements in the upper, middle and lower parasternal regions (95 % confidence), and time for maximum skin reactions (mean and 95 % confidence)
Right field: 5 x 2.43 Gy/week, totally 43.75 Gy in 24 days (measurement points 1, 3, 5)
Left field : 5 x 2.43 Gy/week (10 x 2.43 Gy, gap for 3 weeks, 9.5 x 2.43 Gy) totally 47.40 Gy in 47 days (measurement points 2, 4, 6)

		MEASUREMENT POINT					
		1	2 (upper region)	3	4 (middle region)	5	6 (lower region)
CRE_F		15.20 ± 20	15.20 ± 25	15.20 ± 20	15.25 ± 25	14.75 ± 20	14.85 ± 25
Maximum skin reaction (% of pre-irradiation value)	eryth.	56.0 ± 4.1	53.0 ± 4.2	57.2 ± 4.5	53.2 ± 4.6	50.6 ± 5.6	51.3 ± 5.0
	pigment.	17.6 ± 3.1	13.5 ± 3.2	13.5 ± 3.6	12.1 ± 4.0	14.4 ± 3.6	12.0 ± 4.0
Days after start of irradiation for maximum skin reaction	eryth.	38 ± 2	54 ± 3	39 ± 2	55 ± 3	41 ± 3	55 ± 2
	pigment.	38 ± 2	55 ± 3	40 ± 3	56 ± 3	40 ± 3	57 ± 2

Table 4. Series CRE III. Cumulative radiation effect, and corresponding mean values of spectrophotometric measurements in the upper, middle and lower parasternal regions (95 % confidence), and time for maximum skin reactions (mean and 95 % confidence)
Right field: 5 x 2.56 Gy/week, totally 40.95 Gy in 22 days (measurement points 1, 3, 5)
Left field : 5 x 2,43 Gy/week, totally 38.90 Gy in 22 days (measurement points 2, 4, 6)

		MEASUREMENT POINT					
		1 (upper region)	2 (upper region)	3 (middle region)	4 (middle region)	5 (lower region)	6 (lower region)
CRE_F		14.65 ± 30	13.80 ± 20	14.95 ± 15	14.00 ± 20	14.50 ± 20	13.80 ± 20
Maximum skin reaction (% of pre-irradiation value)	eryth.	48.5 ± 3.7	42.7 ± 7.4	49.6 ± 5.1	46.6 ± 4.7	46.7 ± 6.0	40.0 ± 7.1
	pigment.	16.5 ± 3.2	15.3 ± 3.1	15.9 ± 3.4	15.5 ± 3.4	13.5 ± 4.1	11.7 ± 3.0
Days after start of irradiation for maximum skin reaction	eryth.	36 ± 2	35 ± 2	37 ± 2	38 ± 2	39 ± 2	41 ± 3
	pigment.	37 ± 3	37 ± 2	38 ± 3	40 ± 3	40 ± 2	42 ± 3

Table 5. Series CRE IV. Cumulative radiation effect, and corresponding mean values of spectrophotometric measurements in the upper, middle and lower parasternal regions (95 % confidence), and time for maximum skin reactions (mean and 95 % confidence)
Right field: 5 x 2.54 Gy/week, totally 40.65 Gy in 22 days (measurement points 1, 3, 5)
Left field : 1 x 7.29 Gy/week, totally 29.15 Gy in 22 days (measurement points 2, 4, 6)

		MEASUREMENT POINT					
		1 (upper region)	2 (upper region)	3 (middle region)	4 (middle region)	5 (lower region)	6 (lower region)
CRE_F		14.65 ± 25	14.55 ± 35	15.00 ± 20	15.00 ± 30	14.55 ± 20	14.55 ± 20
Maximum skin reaction (% of pre-irradiation value)	eryth.	52.2 ± 2.7	52.5 ± 3.0	49.3 ± 3.5	50.4 ± 3.5	40.8 ± 4.7	41.3 ± 4.5
	pigment.	16.2 ± 1.9	15.5 ± 1.8	15.7 ± 2.0	14.6 ± 1.7	10.8 ± 1.9	9.9 ± 1.8
Days after start of irradiation for maximum skin reaction	eryth.	36 ± 1	36 ± 1	37 ± 2	38 ± 2	39 ± 2	40 ± 3
	pigment.	36 ± 2	37 ± 2	38 ± 2	38 ± 2	41 ± 3	43 ± 4

Table 6. Series CRE V. Cumulative radiation effect, and corresponding mean values of spectrophotometric measurements in the upper, middle and lower parasternal regions (95 % confidence), and time for maximum skin reactions (mean and 95 % confidence)
Right field: 5 x 2.45 Gy/week, totally 41.65 Gy in 23 days (measurement points 1, 3, 5)
Left field : 5 x (3 x 1.08 Gy/day)/week, totally 54.00 Gy in 23 days (measurement points 2, 4, 6)

		MEASUREMENT POINT					
		1	2	3	4	5	6
		(upper region)		(middle region)		(lower region)	
CRE_F		14.35 ± 10	15.45 ± 20	15.00 ± 10	16.00 ± 15	14.95 ± 10	15.85 ± 15
Maximum skin reaction (% of pre-irradiation value)	eryth.	52.9 - 3.5	57.9 - 2.7	49.0 ± 5.1	55.4 ± 3.6	40.1 ± 6.2	49.2 ± 5.0
	pigment.	17.2 - 1.9	20.1 - 2.8	14.0 ± 1.8	17.9 - 2.4	9.1 ± 3.1	13.0 ± 4.8
Days after start of irradiation for maximum skin reaction	eryth.	37 ± 2	37 ± 3	38 ± 3	38 ± 2	39 ± 4	39 ± 4
	pigment.	37 ± 2	37 ± 2	38 ± 4	38 ± 2	40 ± 4	39 ± 3

DISCUSSION

Fraction size and number of fractions. Field et al (1975) have investigated the early skin reaction in mouse feet for 4, 8, 16 and 32 fractions in a fixed treatment time and found a slope of 0.26 when the total dose was plotted against the number of fractions (in log-log scale), which is in good agreement with the exponent 0.24 proposed by Ellis (1969). The CRE_F (or NSD)-formula also gains support from the experimental data of Douglas and Fowler (1976) for early skin reactions in the mouse for a fraction number between 4 and 30, see Figure 5. However, from the comparison of the doses predicted by the CRE_F (or NSD)-formula and that required for a certain skin reaction in mice in this Figure, it is evident that the exponent 0.24 for the number of fractions results in too high a dose level for a large fraction number. The treatment time was limited to 8 days, making the effect of proliferation negligible in this study.

This is consistent with the result in the series CRE V, in which the early skin reactions to the dose schedule with 50 fractions were significantly stronger than

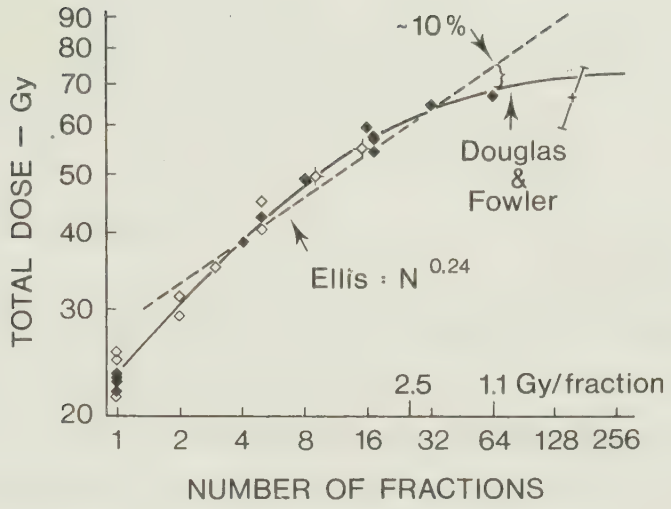


Figure 5. Iso-effect doses as a function of number of fractions predicted by the Ellis' formula (dashed line) and experimentally verified in mouse skin (solid line) for complete repair between fractions and no proliferation. Different symbols refer to varying experimental conditions. (Modified from Douglas and Fowler 1976).

after 17 fractions. The more pronounced early reaction after the 3-times-a-day schedule can probably not be explained by incomplete repair of sublethal damage within the 4-hour interval as the experimental findings of Douglas and Fowler (1976) showed full repair within 3 hours after dose fractions of 1 Gy in mouse skin.

The findings of Dutreix et al (1973) for early reactions in human skin agree approximately with the CRE_F (or NSD)-formula up to 20 fractions. The discrepancy from the other studies is at least partly related to the effect studied. It is therefore more relevant to express the validity of any formula over a range of fraction sizes (see Chapter III) for different biological systems, as the dose per fraction varies with the biological endpoint and the level of damage under study for a constant number of fractions. The deviation of the iso-effect curve from an exponential ($N^{0.24}$) relationship with increasing number of fractions is related to the lower limit of fraction size (exemplified in Figure 5) below which there is no additional

sparing effect from further fractionation. This limit in the fraction size is related to the dose-response of different tissues to small dose fractions (Dutreix et al 1973, Withers 1977).

Treatment time. Evaluation of the importance of varying the overall treatment time is a much more crucial problem in relation to early reactions, being complicated by the influence of homeostatic mechanisms on the cell kinetics during and after multifraction irradiation. The early irradiation response of different tissues involves cell compartments with relatively high proliferative capacity. After accumulated injury, these cell compartments have the ability to increase their proliferation rate either by reducing the cell-cycle time, like basal cells, or by enlarging the proliferative zone, like crypt cells. For the basal cells in epidermis the irradiation-induced shortening in cell-cycle time during a fractionated course is delayed about two weeks (Denekamp 1973) as discussed in Paper II. The reason for this delay is not fully understood.

However, in series CRE II it was found that a gap of 3 weeks required a dose increment of only about 3.7 Gy (340 R) or 8 % of the total dose to counteract repopulation of the basal cells. It could therefore be claimed that proliferation is of secondary importance compared to the number of fractions and the dose per fraction, at least for overall treatment times of less than about 7 weeks.

Early skin reactions with prolonged treatment courses. In Paper IV we presented a study of the early skin reactions with treatment schedules prolonged over more than 90 days. A pilot study was performed with the same technique as in CRE I to V for comparison of the early reaction in normal skin after courses of irradiation with total treatment times of 30 and 90 days, respectively. It was found in this pilot study that the early skin reaction in the slowly treated area was milder than in the rapidly treated one for identical CRE_F as was also confirmed when comparing the skin reactions in patients irradiated for inoperable breast carcinoma by similar fractionation schedules (presented in the same paper).

This milder reaction is probably due to the relatively rapid proliferation of the basal cells and stimulation of the proliferative capacity in this cell compartment which is favoured by a prolonged radiation course. Hence, it is obvious that the CRE_F-formula cannot exactly predict acute skin reactions for very prolonged treatment schedules.

Owing to the verified irradiation-induced changes in repopulation rate in rapid renewal tissues the time factor introduced in the NSD-formula is inappropriate for expressing the influence of overall time on the acute effect of a given dose. Compensation for proliferation for different tisses with a dose increment per day, being a function of treatment time and delivered dose, will be more relevant (Denekamp 1973, Liversage 1971, Dutreix 1974). However, the acute reaction in normal tissue is not the main problem in radiotherapy, since a too severe early response can be eliminated by modifying the fraction size and interval between fractions to allow for repopulation of surviving cells.

CONCLUSIONS

For early skin reactions in humans, the CRE_F-formula, (with special application of the formula for 3 fractions per day) predicts equivalent dose levels, to a standard schedule of daily fractions of 2 Gy with better reliability than 7 % when the different fractionation parameters vary within the following ranges:

- dose per fraction between 1.0 and 7.3 Gy correlated to a number of fractions between 4 and 50, and fixed overall treatment time of 3 to 4 weeks,
- overall treatment time of less than 7 weeks.

This statement is also valid for the NSD-PT-formula and the TDF_F-formula.

THE VALIDITY OF THE CRE_F-FORMULA FOR LATE REACTIONS - CORRESPONDENCE BETWEEN EARLY AND LATE SKIN EFFECTS

In all the papers reviewed in Chapter II the reliability of the CRE_F-formula for predicting biologically equivalent doses for different fractionation schedules was stated only for early skin reactions. Whether or not the CRE_F-formula was also relevant for predicting equivalent late effects in the skin and connective tissue could not be determined at that time.

However, if we regard fractionation as a tool for increasing the tumour control without increasing the morbidity then the late effects on normal tissue are of most relevance in curative radiotherapy. By implication, a model that predicts equivalent late reactions is required. Such a model must be very exact, as for curative purposes the total dose is limited by an accepted degree of risk for complications and a misjudgement in dose of about 5 to 10 % might be disastrous.

In this chapter the results of the follow-up of the patients in some of the series will be presented. These preliminary data allow conclusions about the validity of the CRE_F-formula for a late endpoint. The data have not yet been published but will be discussed here as the follow-up so far has shown that the conclusions based upon early endpoints about the validity of the formula must be revised concerning late endpoints.

PATIENTS AND METHODS

The patients in CRE I were investigated and photographed 30 and 60 months after radiotherapy and patients in CRE IV and V every other month, so far up to 36 and 34 months, respectively. From the photographs, the difference in telangiectasia was scored according to the scale in Table 7.

The score was assigned positive if the effect was most pronounced on the left field and minus in the reverse situation. The scoring procedure is demonstrated by

Table 7. Scoring system for the difference in telangiectasia developed in the two parasternal fields irradiated with different fractionation schedules in series CRE I, IV and V.

0	no difference
1	minimal difference
2	distinct difference
3	very marked difference

Photographs 2 to 4, showing the development of telangiectasia in one of the patients in CRE IV. The scores obtained was analysed by the sign test.

RESULTS

CRE I. Ten of 13 patients in this series were alive 60 months after irradiation. The score for difference in telangiectasia of each patient is plotted in a diagram, Figure 6a, and the average score values are shown in Figure 6b. At 30 months after radiotherapy no significant difference in reaction could be detected, but there was a trend towards a higher degree of telangiectasia after 2 x 4.30 Gy per week than after 5 x 2.25 Gy per week. This difference became slightly more evident and significant at 60 months.

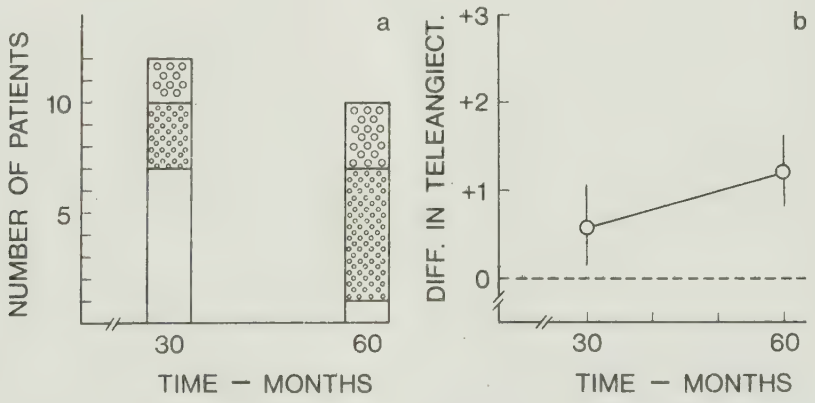


Figure 6. The difference in telangiectasia after 5 x 2.25 Gy/week, totally 47.25 Gy in 29 days and 2 x 4.30 Gy/week, totally 38.70 Gy in 29 days. a) histogram b) mean value with ± 2 SEM. A positive score was assigned to a more pronounced reaction after 4.30 Gy per fraction than after 2.25 Gy.

Photograph 1 shows the patient, who demonstrated the acute reaction to these treatment schedules in Paper I, Figure 7a and 7b, at 60 months. The difference in reaction was scored + 2. The probability of more severe late effects on skin with increasing dose per fraction, in spite of equal CRE_F and identical early skin reactions, became even more obvious during the follow-up of the patients in CRE IV.

CRE IV. Twenty-two out of 27 patients have been followed for 36 months in this series. The reaction score for each patient is plotted in a diagram as a function of time after start of irradiation, Figure 7a, and the average score values are shown in Figure 7b. At 18 months a significantly higher degree of telangiectasia was observed after 1 x 7.29 Gy per week compared to after 5 x 2.54 Gy per week and the difference progressed with further follow-up. This discrepancy in late skin reactions is also demonstrated in Photographs 2 to 4.

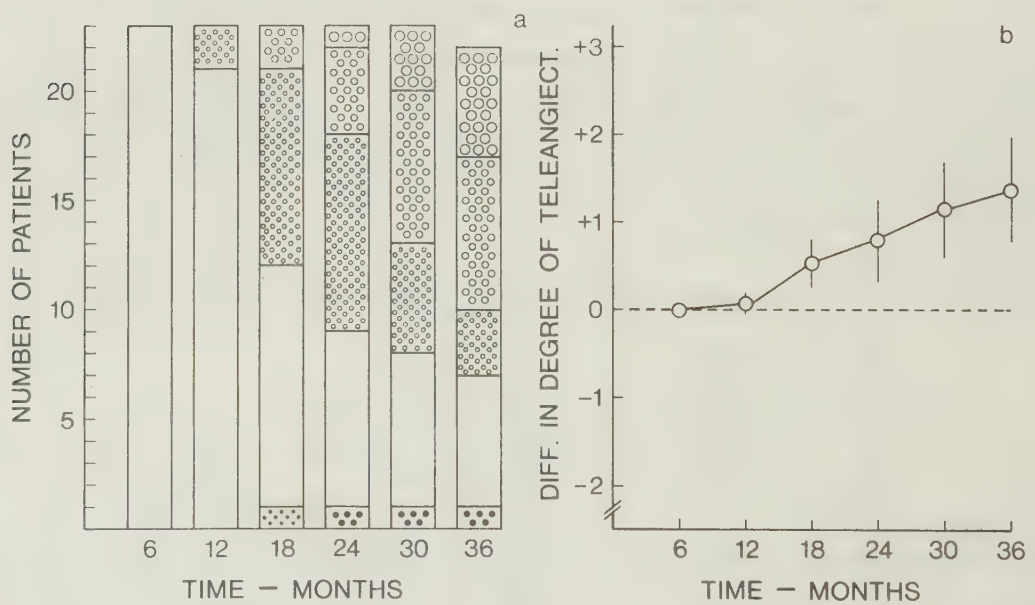


Figure 7. The difference in telangiectasia after 5 x 2.54 Gy/week, totally 40.65 Gy in 22 days and 1 x 7.29 Gy/week, totally 29.15 Gy in 22 days. a) histogram b) mean value with ± 2 SEM. A positive score was assigned to a more pronounced reaction after 7.29 Gy per fraction than after 2.54 Gy.

Photograph 1. Skin reaction 5 years after irradiation. Fractionation schedules: Right field 5×2.25 Gy per week, totally 47.3 Gy in 29 days; left field 2×4.30 Gy per week, totally 38.7 Gy in 29 days. The difference in telangiectasias was scored as +2.

Photograph 2. Skin reaction 12 months after irradiation. Fractionation schedules: Right field 5×2.54 Gy per week, totally 40.6 Gy in 22 days; left field 1×7.29 Gy per week, totally 29.2 Gy in 22 days. The difference in telangiectasias was scored as +1.

Photograph 3. Same patient as in Photograph 2, 18 months after irradiation. The difference in telangiectasias was scored as +2.

Photograph 4. Same patient as in Photograph 2, 30 months after irradiation. The difference in telangiectasias was scored as +3.

It may therefore be concluded that the CRE_F (or NSD)-formula does not predict the dose levels for equivalent late reactions with sufficient accuracy when treatment schedules with a few large dose fractions are used.

CRE V. Ten out of 11 patients have been followed for 34 months in this series. The reaction score for each patient is plotted in a diagram as a function of time after start of irradiation, Figure 8a, and the average score values are shown in Figure 8b. Up to this time a very low frequency of telangiectasia was seen in both fields and there was no difference between the two fields, in spite of the significantly stronger early skin reaction on the field irradiated with 3 x 1.08 Gy/day.

Thus, the difference in CRE_F between the two fields in CRE V, which was found to be consistent with the observed early reaction is not manifested in late skin reactions. This means that the method of using the CRE_F-formula for fractionation schedules in which fractions are repeated several times a day with intervals of only 4 hours (outlined in Figure 4, Chapter II and discussed in Paper III) must be reconsidered. However, this method seems to be valid even for late reactions, as will be discussed below. In Table 8 the data concerning late reactions are summarized.

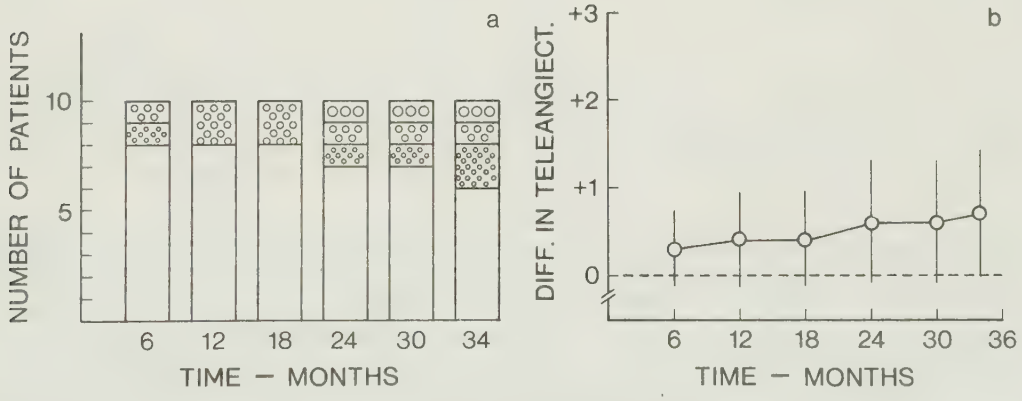


Figure 8. The difference in telangiectasia after 1 x 2.45 Gy/day, totally 41.65 Gy in 23 days and 3 x 1.08 Gy/day, totally 54.00 Gy in 23 days. a) histogram b) mean value with ± 2 SEM. A positive score was assigned to a more pronounced reaction after 1.08 Gy per fraction than after 2.45 Gy.

Table 8. Dose schedules compared on bilateral parasternal fields in the series CRE I, IV and V with modified CRE_F-values for late effects.x)

SERIES	DOSE SCHEDULE	N (fract.)	T (days)	CRE_F	CRE_F (modified)	DIFFERENCE IN LATE REACTION
CRE I	5 x 2.25 Gy/week	21	29	15.8	15.9	YES, significant
	2 x 4.30 "	9	29	15.8	16.5	at 60 months
CRE IV	5 x 2.54 Gy/week	16	22	14.9	15.0	YES, significant
	1 x 7.29 "	4	22	14.9	16.5	at 18 months
CRE V	1 x 2.45 Gy/day	17	23	15.0	15.2	NO, not significant
	3 x 1.08 " 5 times a week	50	23	15.0 (16.0) x)	14.7 (15.7)	at 34 months

x) See paper III

Based on the hypothesis that the acute skin reaction mainly reflects cell-killing to the basal cells of the epidermis - a cell compartment with relatively rapidly dividing cells - and that the late skin reaction, here measured as the degree of telangiectasia, is caused by damage to the slowly proliferating vascular tissues (cf. Arcangeli et al 1974), the conclusions to be drawn from the follow-up of these three series will be:

1) large dose fractions cause relatively more damage to the constituent cells of capillaries than to the basal cells.

2) small dose fractions (about 1 Gy) caused relatively less damage to the constituent cells of capillaries than to the basal cells.

3) the CRE_F-formula must be modified to fulfil the requirements of a model for predicting biologically equivalent total doses for late reactions with different fractionation schedules involving dose fractions between 1 and 10 Gy.

x) CRE_F (modified) refers to a correction introduced on page 33.

DISCUSSION

Modification of the CRE_F-formula

In Paper V we presented an approach for correction of the CRE_F-formula for late reactions based on experimental multifractionation data from different biological systems and endpoints. Only fractionation schedules with 4 or more fractions within 30 days were considered to limit the influence of cell synchrony and proliferation. These data (listed in Table 11, Paper V) were divided into two categories according to the endpoints studied. One group consists of data for early reactions, and the other includes cell and tissue systems showing a delayed reaction.

In Figure 9 the repair increment $D_N-D_1/N-1$, where D_N is the total dose in N fractions that gives an equivalent effect to the single dose D_1, is plotted against the dose per fraction for these data. It will be seen that the repair increments are very well gathered and a straight line could reasonably well be fitted over a limited range in size of dose fraction. The early endpoints (Figure 9a) were mostly for

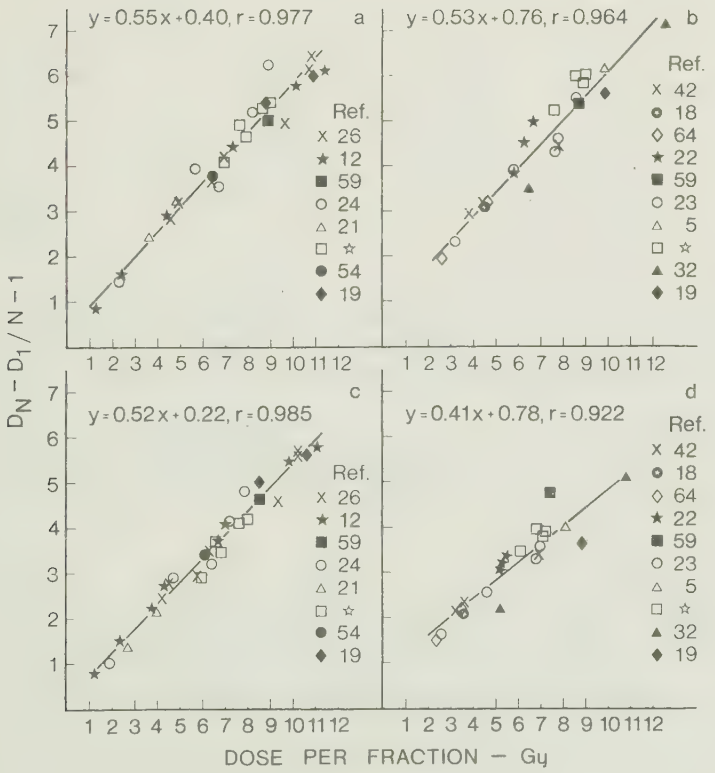


Figure 9.
Repair increments $D_N-D_1/N-1$ as a function of dose per fraction for, a) early endpoints without correction for treatment time, b) delayed endpoints without correction for treatment time, c) early endpoints with correction for proliferation of 0.3 Gy/day, d) delayed endpoints with correction for "slow repair" ($T^{0.07}$). (References see Paper V)

skin, but the late endpoints (Figure 9b) are represented by late spinal cord damage, myocardial fibrosis and lung damage besides late skin damage. This indicates a very similar repair capacity of the constituent cells involved in the late complications of these different tissues. The repair increments are presented without and with (Figure 9c and 9d) correction for proliferation and "slow repair" (Field et al 1976), which influence the early and late endpoints respectively.

In Figure 10 the ratio between CRE_F and the corresponding single dose for equal radiation effects was plotted against the dose per fraction for the same data as in Figure 9. There was no significant correlation for early reactions, with an average ratio of 0.99 ± 0.08 (S.D.); i.e. the CRE_F value expresses the same effect as a single dose of the same magnitude independently of the dose per fraction used in the multifractionation schedule (Figure 10a). However, for the different delayed endpoints a correlation between the ratio, CRE_F/equivalent single dose, and the dose per fraction was established (Figure 10b). The regression line of these data allows correction of the CRE_F-formula for late reactions.

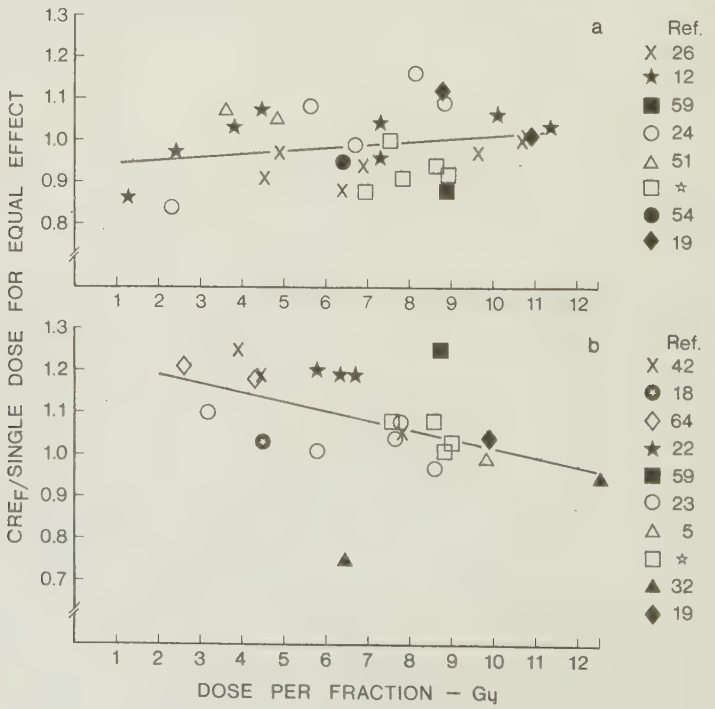


Figure 10.
CRE_F/equivalent single dose as a function of dose per fraction, a) early endpoints, b) delayed endpoints. Regression equation: $Y = -0.0224x + 1.237$, $r = -0.469$ ($p < 0.05$). (References see Paper V)

To make this correction easy to handle in practice, it was normalized to 2.0 Gy per fraction as the most conventional dose fraction. Calculated values of the correction, $L_{(d)}$, for varying dose per fraction are presented in Table 9, and the CRE_F-formula could be made valid for late reactions by the following modification:

$$CRE_F = L_{(d)} \cdot \left(\frac{T}{N}\right)^{-0.11} \cdot d \cdot N^{0.65}$$

Dose per fraction (Gy)	$L_{(d)}$
1.0	0.98
1.5	0.99
2.0	1.00
2.5	1.01
3.0	1.02
3.5	1.03
4.0	1.04
4.5	1.05
5.0	1.06
5.5	1.07
6.0	1.08
6.5	1.09
7.0	1.10
7.5	1.12
8.0	1.13
8.5	1.14
9.0	1.15
9.5	1.16
10.0	1.18

Table 9.
Correction factor $L_{(d)}$ for the CRE_F-formula concerning late effects on normal tissue as a function of dose per fraction.

Example. Biologically equivalent late reactions can be calculated for daily irradiation with 2.54 Gy per fraction ($L_{(d)} = 1.01$) and once-a-week irradiation with 7.29 Gy per fraction ($L_{(d)} = 1.11$) which were employed in the series CRE IV (see Table 8), by means of the equation

$$1.01 \cdot \left(\frac{22}{16}\right)^{-0.11} \cdot 2.54 \cdot 16^{0.65} = 1.11 \cdot \left(\frac{22}{4}\right)^{-0.11} \cdot 7.29 \cdot N^{0.65}$$

$$N = 3.47$$

That is, 3.47 fractions of 7.29 Gy instead of the 4 fractions applied in this series would have resulted in the same degree of telangiectasia as 16 fractions of 2.54 Gy.

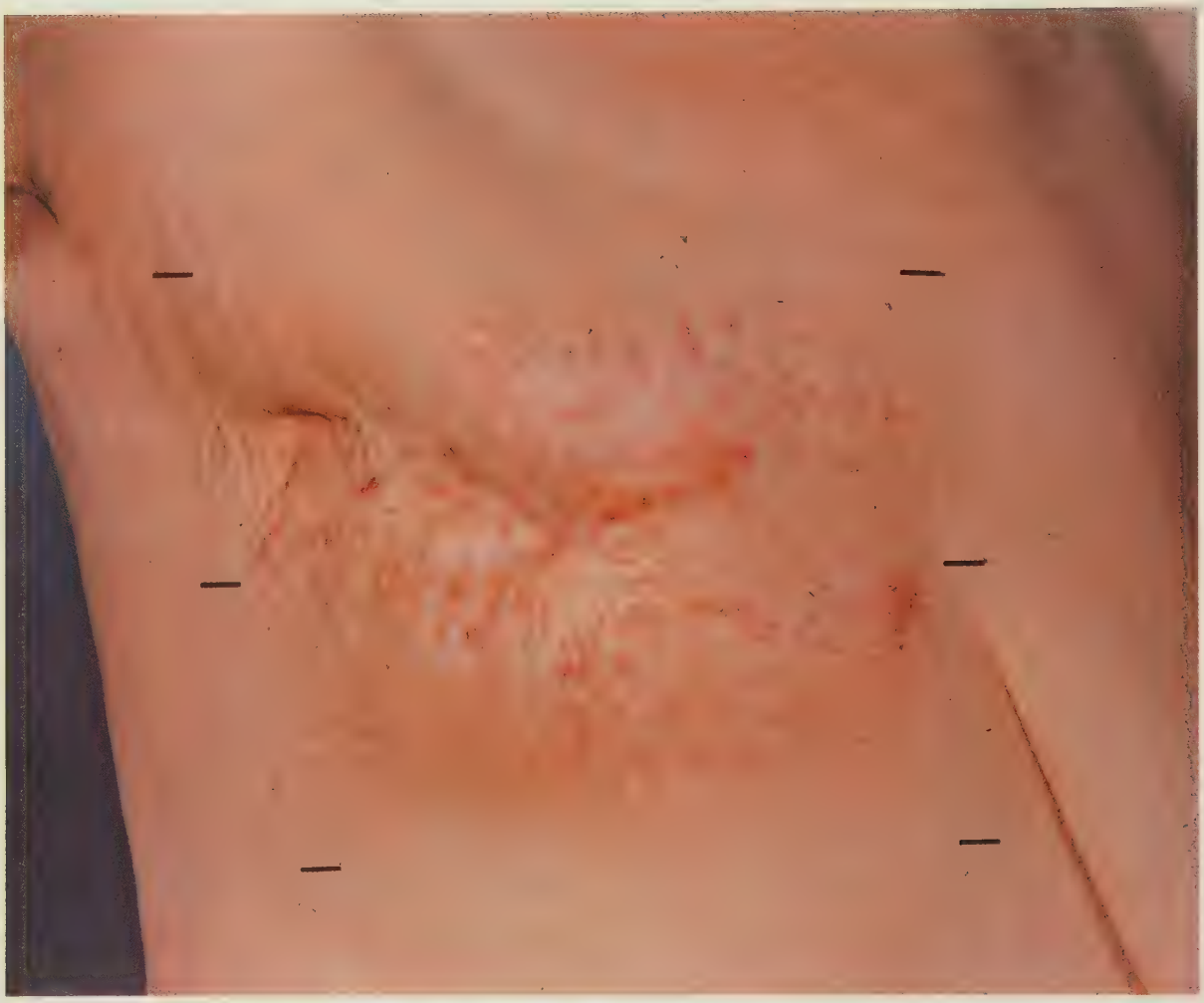
Corrected CRE_F-values for late effects

In Table 8 the CRE_F-values modified according to this correction were also presented for the different series. The differences in CRE_F (modified) were found to be 4, 10 and 3 % for the series CRE I, IV and V, respectively. In CRE IV significant difference in late reaction could be established at 18 months ($p < 0.01$ according to the sign test) and at 30 months this difference was even more accentuated ($p < 0.001$). Up to 30 and 34 months no difference in late effects could be observed in series CRE I and V, respectively. However, in CRE I the skin reactions have progressed to a significant difference at 60 months ($p < 0.01$), which indicates that the correction suggested is at least not too big.

A CRE_F difference in CRE V of 3 % after correction, with either method of calculation for the 3 times-a-day schedule, is consistent with the equal late reactions observed up to 34 months but does not show which is the most correct way of calculating this type of schedule. However, there is a tendency for the more complicated method to be more relevant even for late effects, according to the results shown in Figure 8.

It can also be concluded from the results in this series that the discrepancy demonstrated in Figure 5 between the CRE_F (or NSD)-formula and the measured acute skin reaction in mice for large numbers of fractions will be reduced with respect to late effects. It would therefore be of great value to establish iso-effect curves for late endpoints over a large number of fractions, including small dose fractions (below 2 Gy), to see whether there is any pronounced flattening of the iso-effect dose for large numbers of fractions.

Late effects in skin after prolonged treatment courses. In Paper IV, it was concluded that the early skin reaction was significantly weaker when the overall treatment time was prolonged over 90 days compared to overall treatment times of between



Photograph 5. A patient (Case III) irradiated for an inoperable ductal carcinoma in the entire right breast and lower axilla. Treatment volume was divided into an upper and lower half of equal size for irradiation with different fractionation schedules: Upper area 2×4.50 Gy per week, totally 59.5 Gy in 42 days; lower area 2×2.60 Gy per week, totally 80.0 Gy in 104 days. This Photograph was taken 36 and 38 months, respectively, after irradiation.

30 and 50 days, and that prolonged fractionation increased the therapeutic ratio with respect to the early response of normal tissue. It is interesting to determine however, whether this sparing from acute skin effects will persist during a longer period of observations.

Case II (Paper IV, Figure 7 to 9). Neither on the right nor on the left side of the irradiated thoracic wall of this patient are any late changes at all visible 36 months after irradiation to identical CRE_F of about 18.7.

Case III (Paper IV, Figure 10 to 13). Thirty-six months after the prolonged course of irradiation, see photograph 5, this patient shows a less pronounced difference in telangiectasia compared to the situation 170 days after irradiation (Paper IV, Figure 13). Fibrosis developed between the 6th and 36th months to the same degree, in the slowly irradiated lower area as within the rapidly treated upper area, in spite of the very pronounced difference between the early reactions in the two areas.

According to the correction set-up for the CRE_F-formula for late effects, the two fractionation schedules applied will result in a 4 per cent lower CRE_F value for the prolonged dose schedule, which will hardly yield any pronounced macroscopically distinguishable effect. Contrary to what we found for early reactions, the CRE_F-formula (modified) probably also holds for very prolonged treatment times concerning the late reactions. Hence, the relative sparing from damage to normal skin after prolonged irradiation, that was evident for the acute response, does not exist for the late response.

Comments. During the period of clinical fractionation studies we have noted in several patients that a moist desquamation in a circumscript area is rapidly followed by development of telangiectasia, a finding that was also demonstrated by the patient described above (Case III, Paper IV, Figure 13). A possible interpretation is that the subcutaneous vessels are exposed to mechanical damage due to the loss of epidermis, which may stimulate the proliferation of endothelial cells. The primary radiation-induced damage to vascular tissues, without a preceding moist desquamation,

is not developed until several years after irradiation with the dose levels used clinically.

To my knowledge, no prospective clinical fractionation studies in respect of early and delayed endpoints on normal tissue, have been published so far. However, from a retrospective study of late effects of irradiation on skin and underlying connective tissue Arcangeli et al (1974) draw some conclusions which are supported by our findings:

1. "There is no relation between early and late reactions ..... therefore, early skin reaction is not a good index for predicting or evaluating late injury."

2. "There is some evidence that the severity of late injury is predominantly related to the size of the dose per fraction."

3. "Late radiation injury is not dependent on overall treatment time" (3 to 21 weeks).

One of the conclusions from the follow-up of the skin reaction was that small dose fractions of about 1.0 Gy caused less damage to the constituent cells of the vascular tissues than to the basal cells. This can be explained if the survival curve for the slowly proliferating cells in vascular - connective tissue has a more pronounced shoulder than that for the basal cells. That this probably is so was demonstrated for lung damage compared to the response of skin and gut by Dutreix and Wambersie (1975), who found a less steep initial slope of the survival curve for the constituent cells of lung than for skin and gut.

Another phenomenon that results in relatively more sparing from damage to slowly or non-proliferating cells compared with more rapidly proliferating cells is that of redistribution between repeated dose fractions. The difference is greatest when small doses per fraction are used, as was pointed out by Withers (1975).

CONCLUSIONS

The conclusion about the validity of the corrected and uncorrected CRE_F-formula is related to the effect of a standard schedule with 2 Gy per fraction. For late skin reactions the uncorrected CRE_F-formula is valid with reasonable accuracy for:

- fraction sizes with a small deviation from 2 Gy ($\pm$ 1 Gy)
- overall treatment times up to 100 days

This statement is also valid for the NSD-PT-formula and for the TDF_F-formula.

A correction related to dose per fraction, based upon experimental fractionation data for late endpoints only, was introduced in the CRE_F-formula. The corrected CRE_F-formula was found to be consistent with the results of our clinical investigations on skin for fraction sizes between 1.0 and 7.3 Gy.

In CRE I and IV the fractionation schedules compared showed identical acute skin reactions but significantly different late reactions. The dose schedules compared in CRE V and "the prolonged fractionation study" showed a significant difference in acute reactions but virtually identical late reactions. These findings underline the importance of separating the response of rapid cell renewal tissues from the response of slowly proliferating cell compartments which are probably mainly responsible for late radiation effects and complications such as fibrosis, necrosis and fistulae. The acute reaction therefore does not generally predict the late effect sufficiently exactly to be a guide for dosage in curative radiotherapy.

COMPARISON OF THE RESPONSE TO SINGLE AND FRACTIONATED HIGH DOSE-RATE AND CONTINUOUS LOW DOSE-RATE IRRADIATION

In parallel with dose-fractionation studies on normal tissues for high dose-rate irradiation techniques, study of dose-time relationships for different low dose-rate regimes is also of importance because of similar sparing of normal tissue during irradiation. The radiobiological effects of a high dose-rate schedule contra the effects of continuous low dose-rate treatment are of especial interest owing to the increasing use of afterloading techniques in gynecological radiotherapy.

Continuous irradiation at different low dose rates also offers an alternative to multifractionation regimes at high dose rates for selecting optimal dose-time distributions in external radiotherapy of malignant tumours. Combination of both irradiation techniques sometimes gives very good results.

The CRE-system includes formulae for fractionated high dose-rate irradiation and continuous low dose-rate irradiation, which allow calculation of the cumulative radiation effect on normal tissue for different dose schedules and irradiation techniques (Chapter I, page 8 and 10). [x)]

The experiments presented in Paper V were performed to determine the total doses required for equivalent normal tissue reactions with single and fractionated doses (1.48 Gy/min) and continuous irradiation (1.20 Gy/h). The reaction of pig skin was studied in this investigation. Dose-effect curves were established for the early and medium-term response of pig skin to these different irradiation strategies for determination of:

1) the relative biological effectiveness (RBE) between single doses applied at high and low dose rates, and

2) the correspondence of the CRE_F and CRE_C-formulae, i.e. the normalizing constant, k.

x) $CRE_F = (\frac{T}{N})^{-0.11} \cdot d \cdot N^{0.65}$, $CRE_C = k \cdot D \cdot T^{-0.29}$, or $CRE_C = k \cdot r \cdot T^{0.71}$

where d is the dose per fraction, N the number of fractions, T the overall treatment time, D the total dose, r the dose rate and k the normalizing constant.

The value of the normalizing factor in the CRE_C-formula was determined, assuming that:

a) the CRE_F-model is a good predictor of the total dose required for equal biological effects with different fractionated dose schedules, and

b) the exponent of the time factor in the CRE_C-formula is correct.

The first assumption is based on the findings of the clinical investigations summarized in Chapters II and III, including the correction of the CRE_F-formula for delayed endpoints.

The second assumption implies that the CRE_C-model <u>per se</u> is correct in relating the total dose required for equal effects with different irradiation times or dose rates. The formula can be used for this purpose without knowledge of the value of k. The exponent of the time factor in the CRE_C-model was based upon clinical data for human skin reported by Ellis (1970) and Paterson (1963), and is also supported by data from Mitchell (1960) and experimental studies on pig skin performed by Atkins et al (1972). These data are shown in Figure 11.

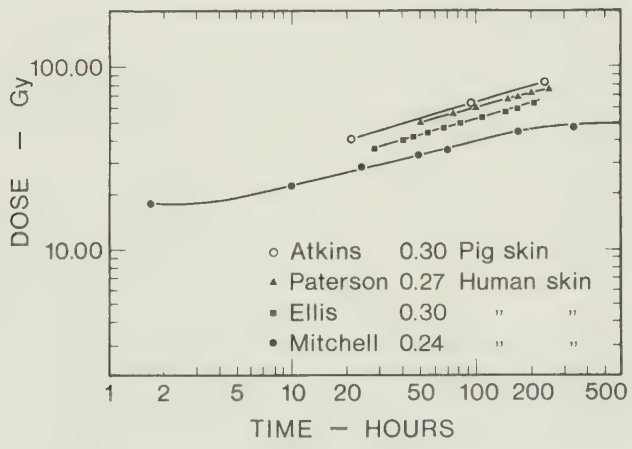


Figure 11. Iso-effect lines for skin reactions to continuous irradiation at different dose rates. The numerical values refer to the slope of the time-dose relationship reported by different authors (Modified from Atkins et al 1972.

MATERIAL AND METHODS

Radiation sources. The experimental design for this comparison was intended to eliminate as many systematic errors as possible. For this purpose two identically constructed plane ^{137}Cs-sources were used with activities of 444 GBq and 4.6 GBq (supplied by the Radiochemical Centre, Amersham). The high-activity source was placed in a specially constructed head of lead and was controlled from outside the treatment room. The low-activity source was fixed to the animal during irradiation in an applicator of aluminium.

Dosimetry. The aim of the dosimetric measurements was to establish:

1) the absorbed dose distribution in one plane parallel to the active surface of the sources,

2) the dose rate at the surface and at a depth of 10 mm,

3) the depth-dose distribution for both sources.

The absorbed dose distribution at a depth of 0.5 mm in a polystyrene phantom measured by film dosimetry is presented in Figure 12. The 90 % isodose was 30 mm in diameter for both sources.

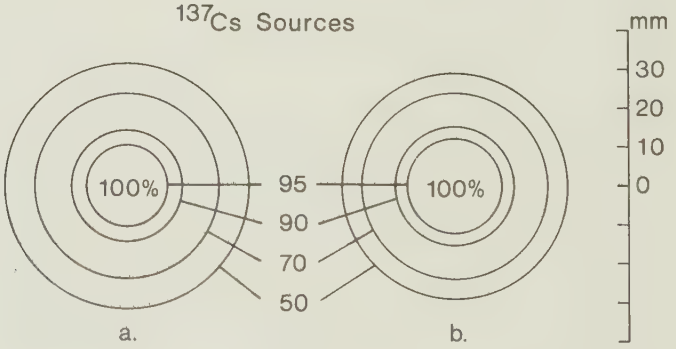


Figure 12.
Field flatness at 0.5 mm depth in a polystyrene phantom a) high dose-rate source, b) low dose-rate source.

Quantitative determinations of the absorbed dose rate at the surface and of the depth-dose distribution were performed with different detectors in a polystyrene phantom. The surface dose, here defined as the dose to a very thin TL-dosemeter placed at

the surface of the phantom in the centre of the field, was found to be 1.48 Gy/min for the high dose-rate source and 20.0 mGy/min for the low dose-rate source.

It was also possible to determine the absorbed dose rate of both sources at a depth of 0.5 mm and 10 mm with a small liquid ionization chamber. The results are given together with extrapolated values at 0 mm in Figure 13.

The depth-dose distribution for the high dose-rate source was determined by TL-dosimetry and was checked with the ionization chambers. For the low dose-rate source the depth-dose curve could be determined quite conveniently with the liquid ionization chamber (Figure 13).

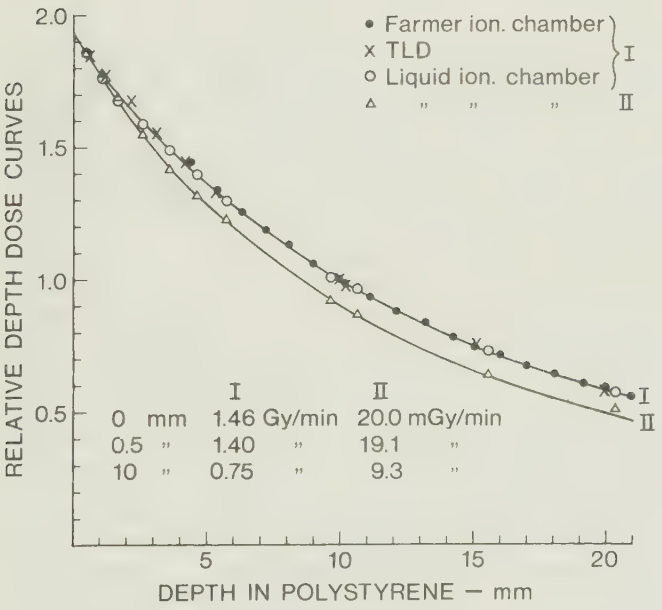


Figure 13.
Relative depth-dose distribution for the high dose-rate source (I) and low dose-rate source (II) at SSD of 10 and 7 mm, respectively, measured with different detectors, and dose rates at 0, 0.5 and 10 mm.

Thus, geometrical arrangements were very similar and considering the field flatness (Figure 12) and the depth-dose curves (Figure 13) no corrections for differences in exposed area or depth-dose distribution between the sources were necessary.

Animals. The skin of immature female and castrated male domestic pigs from a Yorkshire x Swedish Landrace crossbred stock was used for these experiments.

The weight of the pigs varied between 25 and 40 kg when the experiment started and increased by 10 to 20 % over the period of irradiation.

The pigs were irradiated with the high dose-rate source under anaesthesia (thiopentone sodium) at an ambient temperature of $26.5^{o} \pm 1.5^{o}$. The low dose-rate irradiations were performed without anaesthesia and with the source fixed in an applicator sewn onto the skin. The ambient temperature was $21^{o} \pm 1^{o}$.

Dose schedules. The findings in two pilot pigs revealed that the dose levels for continuous irradiation predicted by the CRE_C-formula produced a significantly less pronounced effect than the corresponding dose levels for equal CRE_F-value. It therefore became necessary to establish dose-effect relationships for the different irradiation techniques.

In the main experiment five pigs were irradiated, 2 of them (Pigs N and P) with single doses of high and low dose rates. The other 3 (Pigs Q, R and S) were irradiated with both single and fractionated doses at high dose rate and single doses at low dose rate. The following dose levels were used:

High dose rate: Single doses between 22 and 34 Gy and/or 7 to 8 fractions of 7 to 11 Gy each, every four days.

Low dose rate: Single doses between 40 and 80 Gy.

The exact treatment schedules employed are presented in Paper V.

Skin reaction scoring system. The skin reaction was scored, at least three times a week, according to an arbitrary scale presented in Table 10. Interpolations were carried out between the defined levels.

The reflectance spectrophotometer method used in the clinical investigations was also tried, but was abandoned because the measurements were difficult to evaluate when moist desquamation or necrosis developed. The scoring system also provided the most sensitive method of detecting differences in erythema of the pig skin.

Table 10. Scoring system for early-term and medium-term skin reaction in the pig.

1.0	slight erythema
2.0	erythema
3.0	marked erythema
	moist desquamation
	or necrosis with
3.5	$\emptyset < 10$ mm
4.0	$10 \leq \emptyset \leq 15$ "
4.5	$15 < \emptyset < 25$ "
5.0	$\emptyset \geq 25$ "

In the most typical development of skin reaction two dose-dependent waves can be distinguished: an early reaction and somewhat later a medium-term reaction. The radiation effects after each dose were expressed as the average skin reactions over appropriate time intervals and dose-response curves were constructed. The early reaction for each field was averaged over a 20-day period from the point of time when the reaction reached 30 % of the peak reaction, and the medium-term reaction was averaged over a time interval of 55 days.

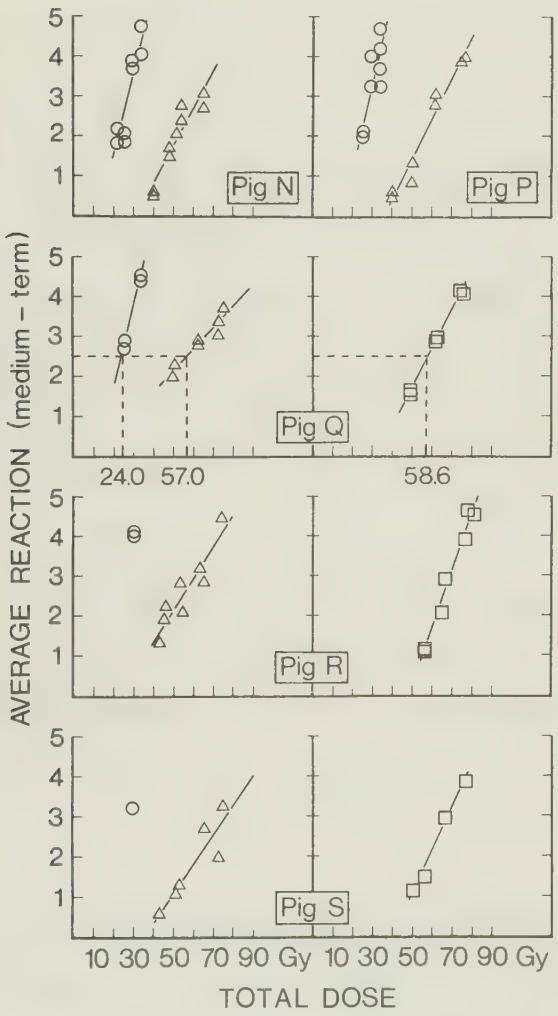
Determination of RBE and normalizing constant. The relative biological effectiveness, RBE, of single doses with low dose-rate (reference) and high dose-rate irradiation was determined from the dose-response curves as the ratio between doses of low dose-rate and high dose-rate irradiation required to produce the same average degree of skin reaction.

The normalizing constant was determined in a similar way from the dose-effect curves for fractionated and continuous irradiation. The $CRE_{F,y}$-value was calculated for the total fractionated dose required for a certain effect level, y, and the total dose, D_y, required with continuous irradiation for the same effect, y, was determined. The irradiation time, T_y, was then calculated for D_y given at a dose rate of 28.8 Gy/day. The value of k was obtained from the equation:

$$CRE_{F,y} = k \cdot D_y \cdot T_y^{-0.29}$$

RESULTS

A straight line was fitted to the dose-effect data obtained with each radiation technique. Figure 14 shows the dose-response curves for the medium-term reaction, with examples of determination of the RBE and the normalizing constant. The RBE values were derived from the ratio of protracted and acute single doses calculated from the dose-effect curves for the average reaction 1.5, 2.5 and 3.5.



Determination of RBE and normalizing factor, k, for Pig Q at the average medium-term reaction 2.5:

$$RBE_{2.5} = \frac{57.0}{24.0} = \underline{2.38}$$

$$CRE_{F,2.5} = 25.9 \text{ (un-corrected)}$$

$$D_{2.5} = 57.0 \text{ Gy}$$

$$T_{2.5} = \frac{57.0}{28.8} = 1.98 \text{ (days)}$$

$$25.9 = k \cdot 57.0 \cdot 1.98^{-0.29} \quad \text{(eq. page 43)}$$

$$k = \underline{0.55}$$

Figure 14. Dose-effect relationship for medium-term reactions to:

○ single doses - high dose rate
△ single doses - low dose rate
□ fractionated doses - high dose rate

Table 11. RBE between the dose rates of 1.20 Gy/h and 1.48 Gy/min determined for the effect levels 1.5, 2.5 and 3.5 of the early and medium-term reactions.

PIG	AVERAGE REACTION early-term			AVERAGE REACTION medium-term		
	1.5	2.5	3.5	1.5	2.5	3.5
N	1.74	1.75	1.75	2.25	2.28	2.31
P	2.07	2.05	2.03	2.36	2.32	2.29
Q		2.29	2.11		2.38	2.61
Mean value	1.97 ± 0.20 (S.D.)			2.35 ± 0.11 (S.D.)		

The mean RBE values were found to be 1.97 for the early reaction, and 2.35 for the medium-term reaction. The RBE values (summarized in Table 11) for early and medium-term reactions differ significantly ($p < 0.01$, according to the sign test). The discrepancies in RBE between different effect levels were found to be very small.

The normalizing constant, k, was calculated in a similar way to the RBE-values from the dose-effect curves. The values of k derived from Pigs Q, R and S, which received fractionated doses by high dose-rate and continuous low dose-rate irradiation, for the average reaction of 1.5, 2.5 and 3.5, gave a mean value of 0.58 for the early reaction and 0.57 for the medium-term reaction (Table 12).

The values of RBE and k were rejected at any degree of reaction that required a substantial extrapolation of either regression line beyond the experimental data for evaluation.

The ratio between CRE_F and the corresponding single dose with the high dose rate for equal reactions could also be determined from the findings in Pigs Q, R and S.

Table 12. Value of the normalizing constant in the CRE_C-formula determined for the effect levels 1.5, 2.5 and 3.5 of early and medium-term reactions.

PIG	AVERAGE REACTION early-term			AVERAGE REACTION medium-term		
	1.5	2.5	3.5	1.5	2.5	3.5
N	.58	.63	.66	.54	.57	.59
P	.53	.57	.60	.53	.57	.60
Mean value	0.60 ± 0.05 (S.D.)			0.57 ± 0.03 (S.D.)		
Q		.54	.56		.55	.53
R	.62	.61	.61	.66	.61	.58
S	.53			.52	.52	
Mean value	0.58 ± 0.04 (S.D.)			0.57 ± 0.05 (S.D.)		

The ratio was found to be very close to unity and, using the relationship, the normalizing constant could also be determined from the dose-effect curves for the single doses given to Pigs N and P.

Including the values of k determined for these two pigs, the mean value of the normalizing constant was found to be 0.59 for the early and 0.57 for the medium-term reaction. These values differ considerably from that of 0.80 proposed by Kirk (1977).

DISCUSSION

The early reaction of the pig skin was characterized by erythema and/or moist desquamation of varying degree. The acute reaction varied considerably in duration. Moist desquamation sometimes healed very rapidly. In other cases healing was prolonged and the reaction proceeded to a second wave, the medium-term reaction, without the acute reaction having completely healed. The medium-term reaction is characterized by erythema or necrosis, depending on the dose levels.

It should be pointed out that the values obtained for the normalizing constant (Table 12) are valid only when a low dose-rate technique is replaced by a high dose-rate technique with a few large dose fractions between 7 and 10 Gy, or vice versa.

Assuming that the acute reaction mainly reflects cell-killing to the relatively rapidly dividing basal cells, and that the medium-term reaction is caused by damage to the slowly proliferating vascular tissues and is thereby a "late endpoint", the modified CRE_F-formula should be used when determining k for the medium-term reaction. As a rather high dose per fraction was used in the present pig experiments, one must expect a stronger medium-term reaction for the same CRE_F than with smaller doses of only 2 Gy per fraction, as discussed in Chapter III. By applying the correction for the CRE_F-formula presented on page 33, the normalizing constant would have been 12 % greater, giving a value of 0.64 instead of 0.57 for the medium-term reaction, if 2 Gy per fraction had been used. Thus, the normalizing constant is 0.59 for early endpoints but a value of 0.64 would be more relevant for late endpoints.

Consequences of the result. Using a normalizing constant of 0.80 in the CRE_C-formula would, according to the findings in this investigation, result in a large overdosage if a continuous low dose-rate radium technique is replaced by a high dose-rate afterloading technique with a few large fractions, and, vice versa, a large underestimation if a high dose-rate technique is replaced by a low dose-rate technique, if the CRE system is used for prediction of biologically equivalent doses.

Two examples will be presented here to demonstrate the method of calculation and the practical effect on prescribed doses of changes in the normalizing constant, k, for converting a low dose-rate technique to a fractionated high dose-rate technique or vice versa. In these examples the quality and volume of radiation are assumed to be the same for both techniques.

EXAMPLE I

A continuous low dose-rate treatment to 30.0 Gy given in 25 h, i.e. at a dose rate of 1.2 Gy/h is to be replaced by a fractionated high dose-rate treatment regime with, for example 1 x 8.0 Gy per week. What total dose should be given for equivalent late effects?

A. Solution according to the originally presented CRE-system

$$CRE_C = k \cdot D \cdot T^{-0.29} \cdot 0.80 \cdot 30.0 \cdot \left(\frac{25}{24}\right)^{-0.29} = 23.76$$

$$CRE_F = \left(\frac{T}{N}\right)^{-0.11} \cdot d \cdot N^{0.65} = 0.83 \cdot 8.0 \cdot N^{0.65}$$

$\left(\frac{T}{N}\right)^{-0.11}$ is approximated to 0.83 for treatment once a week.

As CRE_F should be equal to CRE_C, N is calculated from the equation:

$0.83 \cdot 8.0 \cdot N^{0.65} = 23.76$, $N = 7.1$

i.e., the total dose should be 56.8 Gy

B. Solution according to the findings in the present work

Considering the late effects the normalizing constant is 0.64 and the correction of the CRE_F-formula for a fraction size of 8.0 Gy is 1.13 (Table 9 , page 33).

$$CRE_C = 0.64 \cdot 30.0 \cdot \left(\frac{25}{24}\right)^{-0.29} = 19.01$$

$$CRE_F \quad 1.13 \cdot 0.83 \cdot 8.0 \cdot N^{0.65}$$

As CRE_F should be equal to CRE_C, N is calculated from the equation:

$1.13 \cdot 0.83 \cdot 8.0 \cdot N^{0.65} = 19.01$, $N = 4.2$

i.e., the total dose should be 33.6 Gy

EXAMPLE II

A conventional fractionated high dose-rate irradiation course with 5 x 2.0 Gy/week, totally 60.0 Gy within 6 weeks is to be replaced by continuous irradiation at 1.2 Gy/h, which means 28.8 Gy/day. What total dose should be given for equivalent late effects?

A. Solution according to the originally presented CRE-system

$$CRE_F = \left(\frac{T}{N}\right)^{-0.11} \cdot d \cdot N^{0.65} = 0.97 \cdot 2.0 \cdot 30^{0.65} = 17.70$$

$$CRE_C = k \cdot r \cdot T^{0.71} = 0.80 \cdot 28.80 \cdot T^{0.71}$$

As CRE_C should be equal to CRE_F, T is calculated from the following equation:

$0.80 \cdot 28.80 \cdot T^{0.71} = 17.70$; $T = 0.690$

i.e., the total dose should be 19.9 Gy

B. Solution according to the findings in the present work

Considering the late effects the normalizing constant is 0.64 and the correction of the CRE_F-formula for a fraction size of 2.0 Gy is 1.0 (Table 9 , page 33).

$$CRE_F = 1.0 \cdot 0.97 \cdot 2.0 \cdot 30^{0.65} = 17.70$$

$$CRE_C = 0.64 \cdot 28.8 \cdot T^{0.71}$$

As CRE_C should be equal to CRE_F, T is calculated from the following equation:

$0.64 \cdot 28.8 \cdot T^{0.71} = 17.70$; $T = 0.945$

i.e., the total dose should be 27.2 Gy

Validity of the exponent for the time factor in the CRE_C-formula. In order to verify the time-exponent in the CRE_C-formula, for the present experimental conditions, two pilot pigs (Pigs T and U) were irradiated at dose rates of 1.20 and 0.54 Gy/h and dose-effect relationships were established. This preliminary study, not presented in Paper V, indicated a value of 0.70 and -0.30 for the exponents of this time factor which is in good agreement with the proposed values. The low value of the normalizing constant determined experimentally can therefore not be attributed to another time-exponent in our biological system.

The validity of this exponent means that the total dose must be 40 % higher with continuous low dose-rate irradiation at 0.54 Gy/h compared to 1.20 Gy/h for equivalent biological effects on normal tissue. The RBE between 0.54 Gy/h and 1.48 Gy/min is found by multiplying the RBE values in Table 11 by a factor of 1.4. These facts clearly demonstrate the importance of the total irradiation time in continuous low dose-rate techniques, contrary to the experience of Pierquin (1975), who claims that "There is an isoeffect for continuous irradiation at a low dose rate for dose rates varying between 25 and 100 rads/hours".

Determination of the normalizing constant in the TDF_C-formula. With the same experimental data, the normalizing constant in the TDF_C-formula (see Chapter I, page 10) was determined in the same way and was found to be 2.09 and 2.02 for the early and medium-term reaction, respectively, instead of the proposed value of 1.57 (Orton 1974). No correction for late effects in the TDF_F-model was made here. Contrary to what we found with the CRE system, the application of the TDF-formula with the proposed value of 1.57 for the normalizing constant results in a marked underestimation of the dose if a high dose-rate technique is substituted for a low dose-rate technique, and a large overdosage in the reverse direction.

Normalization procedure. The normalizing procedure in both the CRE and TDF system, to define a biologically equivalent scale for fractionated high dose-rate and continuous low dose-rate irradiation regimes, was based upon the assumption that 60 Gy in 30 fractions over six weeks is biologically equivalent to 60 Gy given conti-

niuously over 7 days in respect of normal tissue tolerance. A correction for volume difference between the two treatment techniques was made in the CRE but not in the TDF system.

The lack of agreement between the calculated equivalent doses with either the CRE or TDF-models and the equivalent doses found experimentally is probably due to one or several of the following factors:

- the definition of normal tissue tolerance,
- ill-defined dose distribution especially with the different low dose-rate techniques used, or
- the difficulty to make a comparison of radiation reactions to both techniques in tissues at anatomically identical sites.

Liversage's formula. Finally, we also checked the relevance of the formula introduced by Liversage 1969 (see Chapter I, page 11) for the purpose of equating continuous low dose-rate and high dose-rate fractionation regimes to our pig-skin result. A comparison between the multifraction doses predicted by this formula and the fractionated doses that corresponded to the continuous low dose-rate irradiations as determined by us, indicated a deviation of less than 10 %, which is within the limits of experimental error.

RBE for early and medium-term reactions. Several possible reasons for the significant difference in RBE between early (1.97 ± 0.20) and medium-term reactions (2.35 ± 0.11) were discussed in Paper V. Some of these were related to differences in repair capacity after small doses (the initial slope of the survival curve) and in redistribution between rapidly and slowly proliferating cells. Considering a low dose-rate irradiation approximated to a multifractionation course of many small dose fractions, the RBE difference between early and medium-term reactions is also consistent with the conclusion (stated on page 30) from the clinical results that "small dose fractions (about 1 Gy) caused relatively less damage to the constituent cells of the capillaries than to the basal cells". These observations also suggest that con-

tinuous low dose-rate irradiation or multifractionation (high dose rate) with many small fractions repeated several times a day might be a suitable irradiation regime for certain rapidly proliferating tumours.

Comment. The determinations of RBE were based upon the dose and dose rate in centre of the field (i.e. at 100 %). To compare our findings of dose-rate effects with those of others, it is necessary to define a reference isodose, for example the 90 % isodose. The RBE values found in this study will then in fact describe the dose-rate effect between 1.08 Gy/h, 0.49 Gy/h and 1.33 Gy/min.

CONCLUSIONS

In a comparison of the effect on pig skin between single and fractionated doses applied at 1.48 Gy/min and continuous irradiation at 1.2 Gy/h under very similar dosimetric conditions, it was found that:

- RBE was 1.97 and 2.35 for early and medium-term reactions, respectively, and
- the normalizing constant in the CRE_C-formula was 0.59 and 0.64 for early and medium-term reactions, respectively.

CLINICAL PROBLEMS IN EVALUATING THE EFFECT OF FRACTIONATION AND DOSE RATE IN RADIOTHERAPY

There is much experimental and clinical evidence that significant benefits can be gained by optimizing fractionation-time-dose relationships. In both mammary carcinoma in the mouse (Fowler et al 1976) and rhabdomyosarcoma in the rat (Fisher and Moulder 1974), a significant difference in cure rate for a given level of normal-tissue reaction can be achieved by proper selection of time-dose parameters. Although an optimal treatment regime for every tumour cannot be defined in clinical practice, owing to the lack of quantitative data for different biological factors, there are many reasons for choosing non-standard schedules instead of conventional daily treatment with 2 Gy

The investigation of the validity of the CRE_F-formula for very prolonged treatment schedules (Paper IV) presents a model for studying the effect on tumours simultaneously with the effect on the normal tissue of two different fractionation schedules. In that paper we concluded that prolonged fractionation with only 2 x 2.6 Gy/week, compared to 2 x 4.5 Gy/week, increased the tolerance of normal skin and thereby the therapeutic ratio with respect to early radiation reactions, as the local tumour control was about the same for both schedules. However, the observation at 3 years (Chapter III) revealed no significant sparing from late damage after the prolonged fractionation compared to our standard schedule. The protracted irradiation technique therefore only allowed application of higher tumour doses without offering any therapeutic benefit with respect to late radiation reactions in normal skin.

For any modification of treatment to be important, it must result in therapeutic benefits, that is, it should increase the effectiveness of the treatment of the tumour without increasing the damage to the dose-limiting normal tissue to the same extent.

When evaluating the effectiveness of a different fractionation schedule for a certain tumour group the following practical clinical questions have to be considered:

1) How well-defined is the relationship between tumour curability and complication rate versus the dose used for the standard fractionation schedule? An idealized model is shown in Figure 15a.

2) How can the radiobiologically equivalent dose in respect of normal tissue be determined for a non-standard schedule?

3) How will the non-standard schedule influence the relationship between tumour control and "the effective dose" expressed in CRE, or any other model for predicting equivalent normal tissue reactions for different dose-time regimes?

4) How can tumour groups with similar characteristics be selected so as to avoid large biological differences between individual tumours (such as growth pattern, histology and tumour size)?

The main problem in finding models for prediction of equivalent biological effects on each critical normal tissue is, in fact, the lack of clinical data concerning the relationships between the complication rate and dose for different irradiation techniques. Moreover, it is only possible to investigate these relationships prospectively over a very limited dose range, for ethical reasons. Morrison (1975) has performed a very careful prospective study on bladder cancer to establish a more optimal tumour dose for these patients. Two dose levels were used for treatment of T_1 and T_2 tumours and two lower dose levels for T_3 and T_4 tumours, with the same number of fractions and same overall treatment time throughout. With these data the tumour control as well as the late complication rate as a function of dose and CRE_F (or NSD) could be established.

Although dependent upon a strict definition of complications, this type of data provides a firm basis for determination of the relevant parameters in more complicated tissue-specific models, like that suggested by Cohen (1971).

In order to establish a relative superiority of one fractionation schedule over another it is necessary to determine the radiobiologically equivalent dose for the tole-

rance of the dose-limiting normal tissue in the non-standard treatment schedule to be tested. This can be done by animal experiments followed by a clinical pilot study or by using models already accepted for clinical applications.

A few possible effects on tumour control of changing the fractionation schedule are schematically illustrated in Figure 15. In relation to the curve T_A for the standard regime, the new tumour control curve, T_B, will be either:

a) displaced to the left (Figure 15b) or right, or

b) steeper (Figure 15c) or less steep.

If the steepness of the tumour control and complication curves for the standard schedule is not precisely known, a study or trial with at least two dose levels for one of the fractionation schedules will give the most adequate answer to the question of whether one dose-time distribution is better than the other (Fowler personal communication). The results obtained with this test situation are exemplified in Figure 15d.

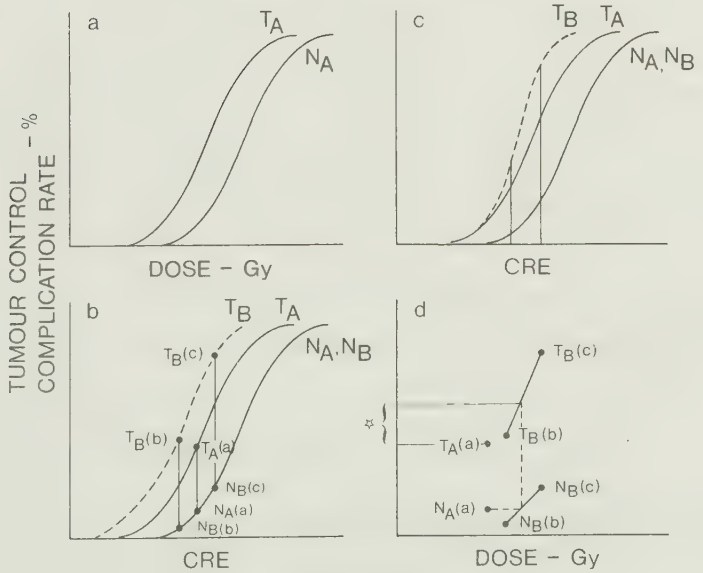


Figure 15.
Outline of the effect on tumour control (T_A, T_B) and the complication rate (N_A, N_B) of two fractionation schedules A and B as a function of dose and CRE. The different dose response curves represent the effect of:

a) the standard schedule, A,
b) the standard, A, and the non-standard, B, schedule; T_B is displaced to the left of T_A, and
c) the schedules A and B; T_B is steeper than T_A.
d) Experimental results from a trial with one dose level, a, for schedule A and two dose levels, b and c, for schedule B.

☆ The therapeutic gain

Owing to the fact that any therapeutic gain may be dependent upon the complication rate (or CRE level) accepted in the investigation, as is best demonstrated in Figure 15c, two dose levels for both irradiation regimes may be necessary in order to draw definite conclusions. However, the difference between the two dose levels must be limited (to about 10 % as a maximum) and can only be justified as long as the optimum dose level is not known, even for the most conventional schedules for the tumour category involved in the study.

A model designed to overcome the individual difference in tumour response is demonstrated in our study of inoperable breast tumours (Paper IV), where the tumour target was divided into two halves and irradiated with different fractionation schedules. A problem is that only certain tumours are suitable for this model.

SUMMARY

The relationship between absorbed dose and biological effect is complex and depends on the fractionation-time-dose distribution, the tissues concerned and the endpoint studied, besides that of radiation quality. The present series of experiments were performed to test the usefulness of the CRE system in predicting the radiobiological effect on normal skin in man and pig for different irradiation techniques.

The following conclusions were based on seven investigations. In each of them two fractionation-time-dose distributions were compared, keeping radiation quality, dose distribution and volume fixed. The biological object of study was always its own control in each series.

The CRE system applies for:

I. Fractionated high dose-rate irradiation

- moderate acute skin reaction, with a reliability better than 7 % over a wide range of fraction sizes (1.0 to 7.3 Gy) and a large fraction number (4 to 50), and overall treatment times of less than 7 weeks

- late skin reaction (telangiectasia) with a reasonable accuracy for fraction sizes with a small deviation from 2 Gy (considered as reference schedule), and overall treatment times up to 100 days

- late skin reaction (telangiectasia) with an introduced correction, related to dose per fraction, for fraction sizes between 1.0 and 7.3 Gy.

II. Continuous low dose-rate irradiation

- with a normalizing factor of 0.59 and 0.64 for early and late skin reactions, respectively.

Under these conditions the CRE system defines an equivalent biological scale for calculating the radiation effect on normal skin over a rather wide range of irradiation regimes, including fractionated high dose-rate and continuous low dose-rate irradiation.

The experimental and clinical data presented in these investigations may be of value for testing future models.

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SKIN REACTIONS AFTER DIFFERENT FRACTIONATION SCHEDULES GIVING THE SAME CUMULATIVE RADIATION EFFECT

INGELA TURESSON and G. NOTTER

During the last decennary the knowledge on cell kinetics and factors influencing the effect of radiation at the cellular level has increased, and consequently better possibilities of understanding the observed radiation response in normal and tumour tissues are offered. The most pressing problem now is to obtain quantitative data on various normal and malignant tissues for calculation of the biologic effect of a fractionated radiation dose.

Time-dose relationships based on clinical observations (STRANDQVIST 1944) and experiments (FOWLER 1965) show that both the radiation dose and the type of fractionation are of decisive importance for the biologic effect. Clinical observations from various fractionation schedules also form the basis of the NSD formula introduced by ELLIS (1967, 1971). This formula was further developed by KIRK et coll. (1971) into a model for calculation of the cumulative radiation effect, CRE.

By means of the CRE system the effect of fractionated irradiation may be estimated in a simplified manner, although only for normal tissue. The CRE varies with the dose per fraction, the number of fractions and total duration of therapy, according to the formula:

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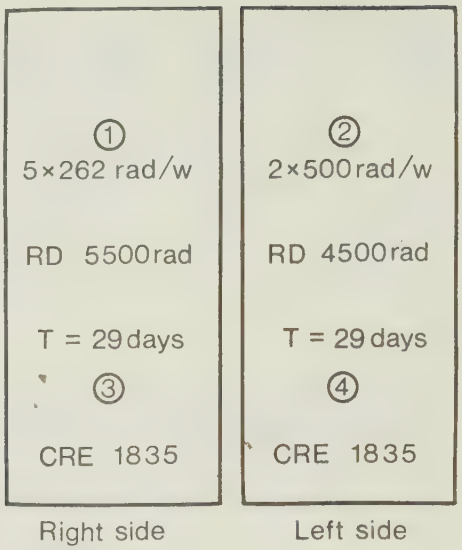


Fig. 1. Schedule for bilateral treatment of the parasternal region with electron radiation (13 MeV). On the marked regions 1, 2, 3 and 4 reflectance spectrophotometer measurements were performed.

$$CRE = \left(\frac{T}{N}\right)^{-0.11} \cdot d \cdot N^{0.65}$$

where N is the number of treatments of d rad evenly distributed over T days. In the formula above ^{60}Co radiation is considered as reference and thus the relative biologic effectiveness, RBE, is equal to 1. (The dimension of CRE is $rad \cdot days^{-0.11}$, which has been called 'reu', the radiation effect unit. The unit has been excluded from this report pending a new proposal from ICRU.) In the formula, N is assumed to represent the influence of repair of sublethal damage and T the influence of cell repopulation. The CRE value corresponding to the tolerance level is considered to be constant for a given type of normal tissue and a given volume, originally proposed by Ellis in the NSD model (1968). These CRE levels may, however, vary between different centers due to variations in criteria of tolerance.

Table 1

Variations in reflectance spectrophotometer measurements in 3 different series; 10 measurements in each series

Skin	Wavelength nm	Mean value scale divisions
Non-irradiated	578	33.9 ± 0.9
(series A)	660	58.8 ± 0.5
Irradiated	578	24.1 ± 0.8
(series B)	660	55.3 ± 0.4
Non-irradiated	578	34.4 ± 1.0
(series C)	660	58.3 ± 0.3

The CRE formula is also defined at the subtolerance level, unlike the NSD formula (Ellis 1969). The CRE and NSD values are therefore only numerically comparable at the limit of normal connective tissue tolerance. We have chosen to use the CRE concept because it allows more straight-forward handling. The CRE instead of the NSD is therefore referred to in the present report, although the discussion below is valid for both systems.

Before using formulae like the CRE system in clinical routine, it is necessary to prove their reliability experimentally under controlled clinical conditions. The present work reports such a test comparing the biologic effect of 2 different treatment schedules with 2 and 5 irradiations respectively per week under otherwise identical conditions.

Material and Methods

Thirteen patients with mammary carcinoma were irradiated postoperatively in the parasternal region bilaterally, field size 5 cm × 12 cm. The series was designed to give identical CRE values of 1 835 for both fields, although they were irradiated with different types of fractionation. On the left side 2 irradiations were given per week, totally $9 \times 500 = 4\,500$ rad (reference dose)* i.e. N = 9 and T = 29 days. The right side was irradiated daily, 5 times per week during the same time period (29 days), i.e. 21 irradiations. The dose per fraction d for equivalent CRE values to the two areas of irradiation was calculated by means of the equation

$$\left(\frac{29}{9}\right)^{-0.11} \cdot 500 \cdot 9^{0.65} = \left(\frac{29}{21}\right)^{-0.11} \cdot d \cdot 21^{0.65} \qquad d = 262 \text{ rad}$$

The total dose given to the right-hand field was 21×262 rad $= 5\,500$ rad (reference dose) i.e. N = 21 and T = 29 days (Fig. 1).

The biologic effect of the irradiation was estimated by measuring the skin erythema and pigmentation. Both were recorded by means of a photoelectric reflection meter (Photovolt, Model 670). An area of approximately 2.5 cm² was illuminated with light of wavelength 578 nm, width 8 nm at half maximum received by interference filter (Chu et coll. 1960). Light of this wavelength is absorbed by oxyhaemaglobin. The reflected light was read (in scale divisions). The increase of pigmentation resulting from the treatment was registered in the same manner but with light of wavelengths above 660 nm, received by a gelatin filter with cut of at 660 nm. Measurements were performed twice weekly commencing before the first treatment. In addition, the patients were photographed once a week. Previous investigations had shown that radiation erythema is generally more marked above the second intercostal space than below it, due to a difference in sympathetic tone in this region (Adams-Ray 1952, Notter et coll. 1965). The measurements were therefore performed at 4 points, numbered 1 to 4 (Fig. 1), thus enabling comparison of the anatomically equivalent regions 1 and 2, 3 and 4, respectively.

* The reference dose (RD) is equal to the peak absorbed dose

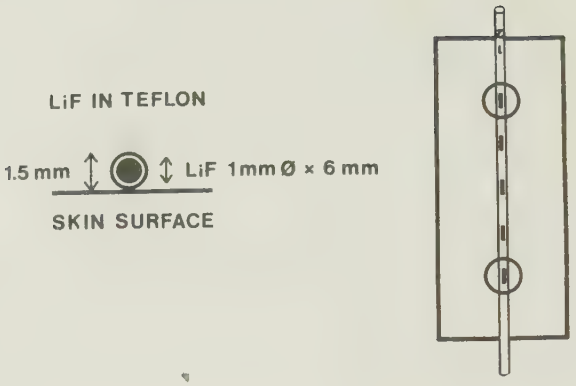


Fig. 2. Skin dose measurements with LiF in teflon probes. The upper dosimeter was placed within measurement field 1 and 2 and the lower within field 3 and 4.

All measurements are stated with limits of error equivalent to 95 per cent confidence interval.

The precision of measurements at the same occasion was determined by 10 repeated measurements in one patient for reflectance (in scale divisions) from non-irradiated skin, series A, and for irradiated skin, series B. The magnitude of normal variations caused by, for example, variations of temperature, was registered in a control subject by means of 10 measurements performed during a period of 3 months, series C (Table 1).

The extent of the limits of error in A is determined solely by the precision of measurement. In B the erythema can also influence the measurement and in C variations in the individual from one occasion to another will influence the results as well as

Table 2

Mean values of skin doses as per cent of the reference dose. Measurement points 1 and 3 correspond to the mean value of 21 determinations and measurement points 2 and 4 to the mean value of 9 determinations

Patient No.	Measurement point			
	1	2	3	4
1	81.4±3.1	83.2±4.6	84.2±3.1	82.4±6.8
2	81.6±3.5	84.3±2.6	84.7±3.7	85.2±3.2
3	85.5±3.9	83.6±6.5	83.4±2.3	85.6±5.2
4	84.1±4.3	86.0±4.2	83.9±3.8	84.9±3.4
5	80.6±5.4	83.1±5.6	84.2±4.2	87.7±4.5
6	83.1±3.5	81.4±3.8	85.6±3.9	83.9±2.1
7	88.6±4.1	87.4±4.5	88.4±3.7	89.0±4.0
8	89.0±3.3	89.1±4.8	89.8±3.7	90.9±5.1
9	86.4±2.9	87.5±3.5	86.2±2.5	88.7±3.7
10	89.4±2.5	86.2±5.8	90.2±2.9	85.6±5.2
11	88.5±5.3	85.2±9.3	89.0±5.3	87.2±7.0
12	88.7±2.6	87.1±6.0	91.7±5.0	89.0±4.9
13	85.6±3.0	87.1±5.6	87.1±2.2	87.1±3.6

Table 3

Mean values of skin doses at the 4 measurements points in Table 2 and corresponding cumulative radiation effect (CRE)

Measurement point	Mean value per cent	CRE
1	85.6±1.9	1 570±35
2	85.6±1.3	1 570±25
3	86.8±1.6	1 595±30
4	86.6±1.5	1 590±30

precision of measurement. Agreement between the limits of error in the 3 series was good (Table 1). The accuracy in one reflectance determination is thus mainly dependent upon the precision of the measurement technique.

In connection with each irradiation TLD determinations were performed (Fig. 2) including determinations at points 1 to 4 which were used for reflectance measurements (LINDSKOOG 1974). The fields were irradiated with electrons (13 MeV) from a betatron (BBC Asklepitron 35). The relative dose difference between the two fields for each patient proved to be small and practically negligible (Table 2). The mean value of the average skin doses as per cent of the reference dose for all patients was then calculated and the result appears in Table 3.

The electron density of the dosimeters is $6.17 \cdot 10^{23}$ cm^{-3} while the electron density of soft tissue is $3.41 \cdot 10^{23}$ cm^{-3}, and we therefore estimate that the dosimeter integrates the absorbed dose within the effective depth of 0.25–1.0 mm (MARKUS 1969). Preliminary results of central deep dose measurements with LiF (1 mm × 0.1 mm) show that the dose in electron irradiation (13 MeV) is constant at depths less than 1 mm (TURESSON, unpublished data). The doses found are therefore considered significant for the absorbed dose at approximately 0.1 mm depth to the basal cells responsible for renewal of the epidermis and to the subpapillary capillary net at less than 0.5 mm depth, which mainly determines the colour of the skin.

Results

Reflectance determinations at the four measurement points were analysed separately for each patient. The change in the reflectance values during the period of treatment was normalized on the basis of the initial value before irradiation, i.e. the value for non-irradiated skin. An example of results of measurements in the same patient is illustrated in Figs 3 and 4 and the mean values for all patients are presented in Figs 5 and 6. Erythema and pigmentation developed concomitantly and on the whole in parallel. Both reactions were somewhat less marked, and became maximal some days later, in the lower parasternal region compared to the upper. In the upper region the maximal skin reaction was observed 8 to 14 days after the end of treatment, i.e. 37 to 43 days after the commencement of radiation therapy, irrespective of

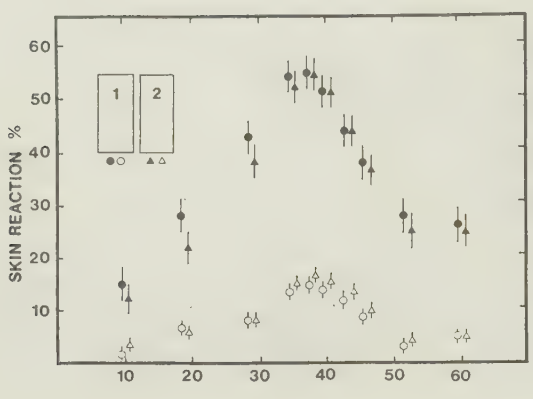


Fig. 3

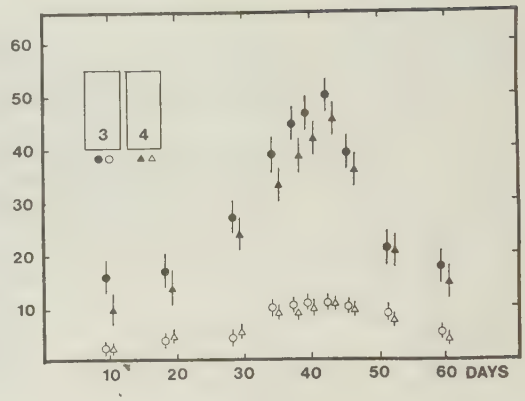


Fig. 4

Fig. 3. Results of reflectance spectrophotometer measurements of skin erythema (wavelength 578 nm) and pigmentation (wavelength 660 nm) in a patient, in the upper parasternal region. Measurement point 1, 5 × 262 rad per week and RD = 5 500 rad; measurement point 2, 2 × 500 rad per week and RD = 4 500 rad. The treatment series were completed at 29 days. Black symbols indicate erythema, white symbols pigmentation.

Fig. 4. Results of measurements in the lower parasternal region in the same patient as in fig. 3. Measurement point 3, 5 × 262 rad per week and RD = 5 500 rad; measurement point 4, 2 × 500 rad per week and RD = 4 500 rad. (Symbols as in Fig. 3.)

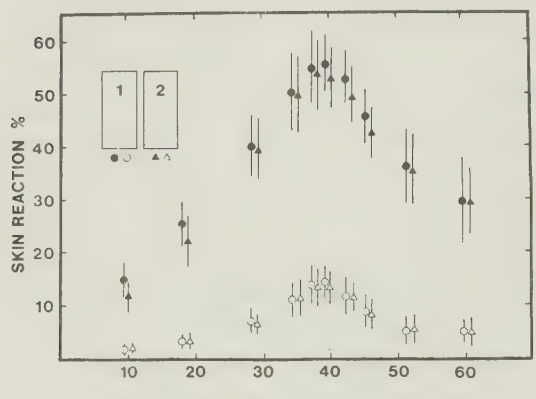


Fig. 5

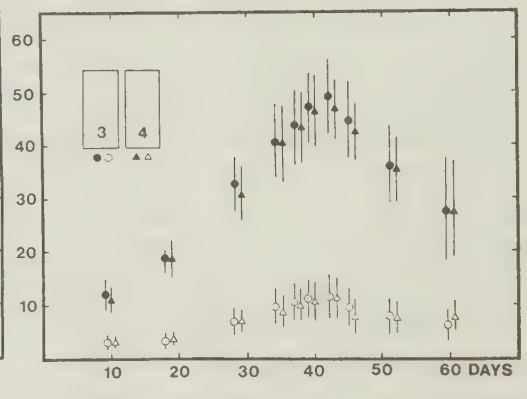


Fig. 6

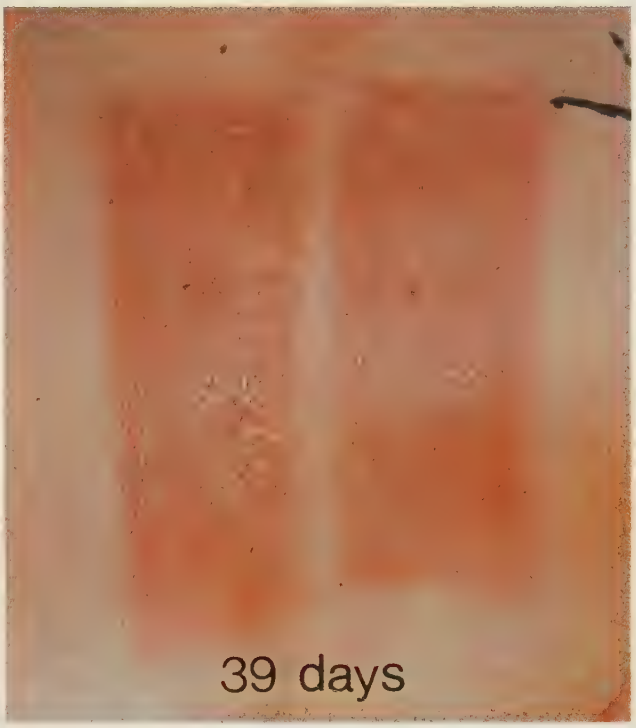
Fig. 5. Mean value of reflectance spectrophotometer measurements for erythema (wavelength 578 nm) and pigmentation (wavelength 660 nm). Measurement point 1, 5 × 262 rad per week and RD = 5 500 rad; measurement point 2, 2 × 500 rad per week and RD = 4 500 rad. The treatment series were completed at 29 days. (Symbols as in Fig. 3.)

Fig. 6. Results of measurements in the lower parasternal region in the same patients as in Fig. 5. Measurement point 3, 5 × 262 rad and RD = 5 500 rad; measurement point 4, 2 × 500 rad and RD = 4 500 rad. (Symbols as in Fig. 3.)

the type of fractionation (Fig. 5). In the lower region (Fig. 6). erythema did not become maximal until 11 to 16 days after the completion of treatment i.e. 40 to 45 days after commencement of the irradiation.

The limits of error in the diagram are mainly due to variations in the response to radiation from patient to patient. All patients developed a dry erythema, bordering on an exudative reaction, in the center of the field where the dose was approximately

a



b

Fig. 7. Skin reaction at end of treatment; **a)** T=29 days, and **b)** maximal reaction 10 days later, T=39 days. Fractionation schedules: Right field 5×262 rad per week and RD=5 500 rad; left field 2×500 rad per week and RD=4 500.

Fig. 8. Pigmentation in one of the patients five months after treatment. Fractionation schedules as in Fig, 7.

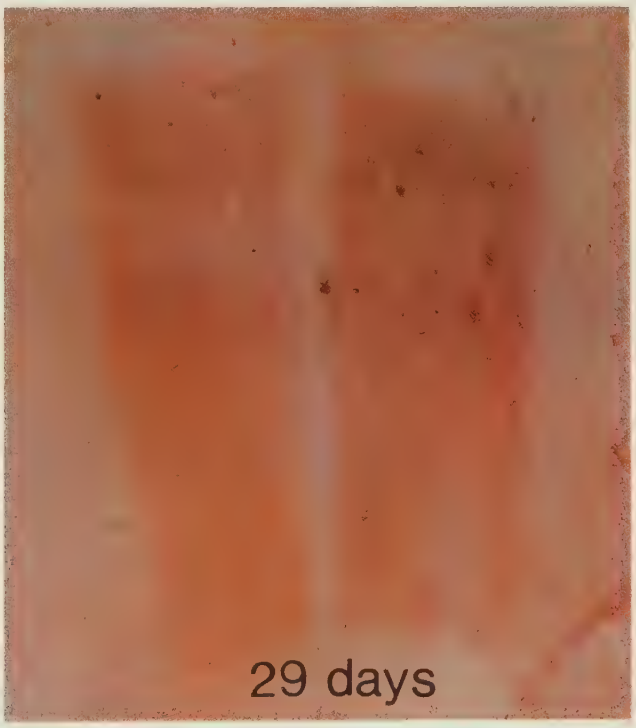


Fig. 12. Skin reaction at the end of treatment, T=29 days. Fractionation schedules: Right field 2×475 rad per week and RD=4 275 rad; left side 2×500 rad per week and RD=4 500 rad.

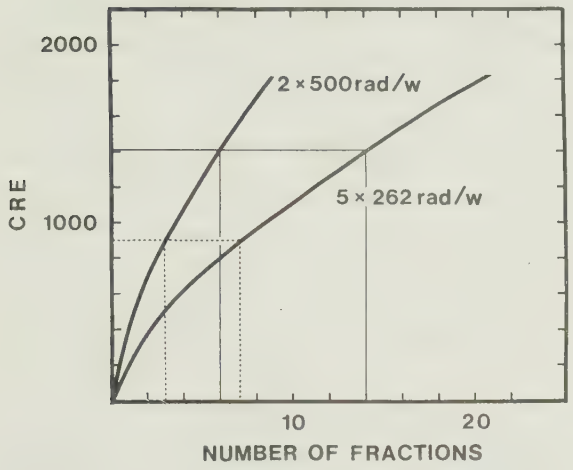


Fig. 9. Cumulative radiation effect, CRE, as a function of the number of fractions N during treatment twice per week and five times per week, respectively, $(T/N)^{-0.11}$ has been approximated to 0.88 and 0.97, respectively,

5 per cent higher. The photographs in Fig. 7 and 8 also show identical erythema and pigmentation in normal skin after the two different fractionation schedules at various time intervals.

Discussion

The result demonstrates the possibility of correct iso-effect calculation with the CRE formula in different types of fractionation. This test proves the validity of the formula when a treatment time of 29 days is combined with a dose per fraction of 262 rad and 21 treatments, or 500 rad and 9 treatments, for the early reactions, skin erythema and pigmentation.

The skin reactions developed simultaneously and were evident 10 days after the first treatment. Both the erythema and pigmentation were maximal in the upper parasternal region 37 to 43 days after the commencement of irradiation and in the lower parasternal region 40 to 45 days after beginning of treatment. Both reactions were somewhat less marked in the lower part of the radiation field compared to the upper part, which was in agreement with previous experience (NOTTER et coll. 1965).

The extent of the skin reactions in the irradiated patients varied within narrow limits. These observations are in contrast to the general impression that radiation erythema varies greatly in different patients, thus being unsuitable for evaluation of an early radiation effect.

Fig. 9 illustrates how the cumultive radiation effect increases with the number of fractions during the two treatment series. The figure also shows that the radiation effect per fraction declines successively during the period of treatment. This property of the CRE model is not valid for the NSD formula, for which the effect per fraction is considered constant and is expressed as partial tolerance, PT (WINSTON et coll. 1969). The two models are therefore not comparable at the subtolerance level.

In Fig. 9 are marked two examples of CRE levels reached at the same time in both fields. CRE = 900 corresponds to N = 3 with two fractions weekly and N = 7 with

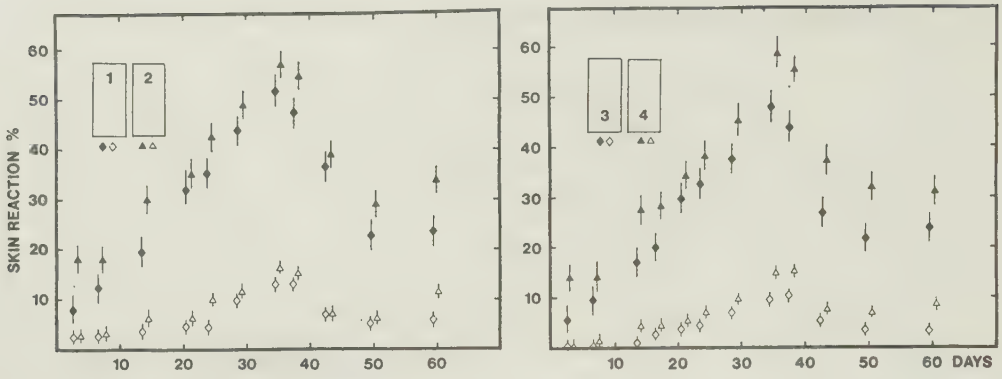


Fig. 10 Fig. 11

Fig. 10. Results of reflectance spectrophotometer measurements of skin erythema (wavelength 578 nm) and pigmentation (wavelength 660 nm) in the same patient in the parasternal region. Measurement point 1, 2 × 475 rad per week and RD = 4 275 rad; measurement point 2, 2 × 500 rad per week and RD = 4 500 rad. The treatment series were completed at 29 days. (Symbols as in Fig. 3.)

Fig. 11. Results of measurements in the lower parasternal region in the same patient as in fig. 10. Measurement point 3, 2 × 475 rad per week and RD = 4 275 rad; measurement point 4, 2 × 500 rad per week and RD = 4 500 rad. (Symbols as in Fig. 3.)

five fractions weekly, thus given in T = 9 to 10 days. CRE 1 410 corresponds to N = 6 and N = 14 respectively, when T = 19 to 20 days. However, equal CRE values during the radiation treatment are not simultaneously related to identical skin reactions as these are delayed. It is therefore difficult to compare the reactions during the period of treatment itself and to assess the results at the last occasion of treatment. It is important that this be borne in mind when drawing conclusions from retrospective investigations.

In order to gain an impression of the variation of the skin reactions with dosage, the right and left parasternal regions of 2 patients were treated as follows: right field 2 × 475 rad per week to a total dose of 4 275 rad, left field 2 × 500 rad per week to a total dose of 4 500 rad, which means a deliberate difference in dosage of 5 per cent. The dosage difference determined in one patient was only 3 per cent and the reaction was the same in both fields. The results of reflectance measurements in the other patient (Figs 10, 11) illustrate the effect of a measured dosage difference of 6 to 7 per cent. Visually, the difference in reaction between the fields was obvious and greater than in any of the patients in the CRE test (Fig. 12). This result together with the more marked reaction in the center of the field at approximately 5 per cent higher dose suggests the dose-dependence of the effect on the skin and also indicates the precision with which it is possible to verify the CRE model. The method of measurement is highly reproducible and the sensitivity is fully comparable with that of the eye. It is therefore considered that reflectance spectrophotometer measurement offers a useful method for quantification of erythema and pigmentation. Whether or not these early reactions are relevant for calculations of late effects in the skin and connective tissue is, however, a different question and cannot at the moment be decisively answered (Arcangeli et coll. 1974, Ellis 1968, Fowler 1969).

The hypothesis that the capillary endothelium as a common target in different organs perhaps is most important for the determination of the radiation tolerance is becoming more and more accepted. This opinion has experimental support in an electron microscopic investigation of heart, skeletal muscle, lung and kidney in rats (PHILLIPS et coll. 1972). The microcirculation is more or less well developed in different structures depending on the metabolic activity or need for an effective and rapid hemic interchange. The functional tolerance levels for different organs may well be strongly related to the tolerance of parenchymal cells to injury of their microcirculation, exemplified with the low tolerance dose of the kidney. If this is true, then the tolerance levels of specific normal tissues could be expressed with different CRE levels.

The NSD formula, probably better known than the CRE formula, has been criticized for being based on an extrapolation of too few and uncertain clinical data. Increased experimental and clinical investigations of the CRE model are therefore indicated. The present investigation exemplifies how the CRE formula may be used for prospective calculation of biologically equivalent doses for different treatment schedules. This enables objective description and comparison of differences in radiation effect between normal and malignant tissue in various fractionation schedules. Although the tumour effect cannot be calculated it is possible in both retrospective and prospective investigations to correlate the therapeutic results of irradiated tumours to the CRE for the normal tissues within the target volume.

SUMMARY

The CRE formula was used for calculation of biologically equivalent radiation doses with different fractionation schedules. The early radiation effects, skin erythema and pigmentation were measured with a reflectance spectrophotometer at wavelengths 578 and 660 nm. The course and maximum for both erythema and pigmentation agreed well with the two types of fractionation. The results seem to justify further use of this simple formula.

ZUSAMMENFASSUNG

Die CRE Formel wurde für Berechnungen der biologisch äquivalenten Strahlendosen bei verschiedenen Fraktionierungs-Schemata verwendet. Die frühzeitigen Strahleneffekte, Haut-Erythem und Pigmentierung, wurden mit einem reflektierenden Spektrophotometer bei einer Wellenlänge von 578 und 660 nm gemessen. Verlauf und Maximum für sowohl Erythem und Pigmentierung stimmten gut mit den beiden verwendeten Fraktionierungs-Typen überein. Die Ergebnisse dürften den weiteren Gebrauch dieser einfachen Formel rechtfertigen.

RÉSUMÉ

La formule CRE a été utilisée pour calculer les doses de radiation biologiquement équivalentes avec différents schémas de fractionnement. Les effets précoces des radiations, l'érythème cutané et la pigmentation ont été mesurés avec un spectrophotomètre à réflectance

pour des longueurs d'ondes 578 et 660 nm. L'évolution et le maximum de l'érythème et de la pigmentation sont en bonne concordance avec les deux types de fractionnement. Ces résultats semblent justifier qu'on continue à utiliser cette formule simple.

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SKIN REACTION AS A BIOLOGIC PARAMETER FOR CONTROL OF DIFFERENT DOSE SCHEDULES AND GAP CORRECTION

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Biologic effects on normal tissue for fractionated irradiations can be calculated by the Cumulative Radiation Effect (CRE)-formula (KIRK et coll. 1971):

$$CRE = \left(\frac{T}{N}\right)^{-0.11} \cdot d \cdot N^{0.65}$$

The formula describes the biologic effect on normal tissue for fractionated irradiation when T is the treatment time in days, N the number of fractions and d the dose per fraction in rad defined for ^{60}Co radiation. The formula has previously been used for prospective dose calculations of daily and 'twice a week' irradiation on bilateral parasternal fields in patients operated upon for carcinoma of the breast (TURESSON & NOTTER 1975). The result showed that the CRE-formula was useful for prospective calculation of biologically equivalent radiation doses with different fractionation.

With the increasing use of varying gaps during irradiation courses it is essential to modify the total dose with reference to the recovery and especially the repopulation of the normal tissues. ELLIS has, for calculation of gaps in the NSD-formula, proposed the correction $(T/T+G)^{0.11}$, where T is the number of treatment days be-

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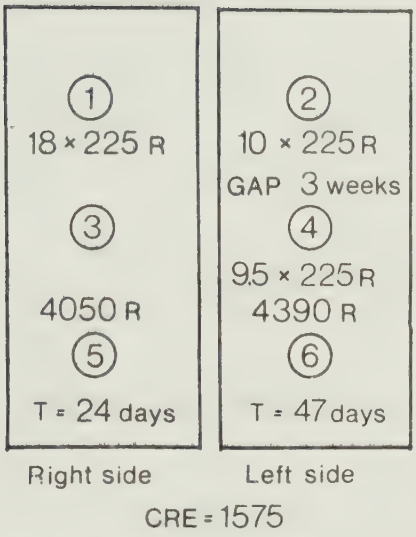


Fig. 1. Treatment schedule for bilateral treatment of the parasternal region with 200 kV roentgen rays (HVL 1.2 mm Cu). On the marked regions (1 to 6) reflectance spectrophotometer measurements were performed.

fore a gap of G days (ELLIS 1969, WINSTON et coll. 1969). Recently KIRK et coll. (1974) have presented a gap correction to the CRE-system. This correction is $e^{-0.008\,G}$, where G is the number of days the gap lasts. The two corrections will be discussed later on.

In the present analysis ELLIS' gap correction in the CRE-formula is used. If the subtolerance level after the first part of the treatment of T days, before a gap of G days, is expressed as CRE (I), and the reduced effect after the gap is called CRE (II), then:

$$\text{CRE (II)} = \text{CRE (I)} \cdot \left(\frac{T}{T+G}\right)^{0.11}$$

Thus, CRE (II) describes the radiation effect just before starting the second part of the treatment.

The biologic effect of different prospectively calculated dose schedules was controlled by the same technique of reflectance spectrophotometer measurements as previously (TURESSON & NOTTER).

If skin reaction as a biologic parameter for the radiation effect is used to evaluate the reliability of the CRE-function, the radiation sensitivity of the skin and the accuracy of the spectrophotometer measurements must be known. Therefore in the present series the minimum dose difference causing a measurable difference in erythema and pigmentation has been investigated.

Material and Methods

To investigate the gap-correction 14 patients with mammary carcinoma (of whom 4 were operated upon the left and 10 on the right side) were irradiated postoperatively on bilateral parasternal fields of 5 cm × 12 cm with 200 kV roentgen rays

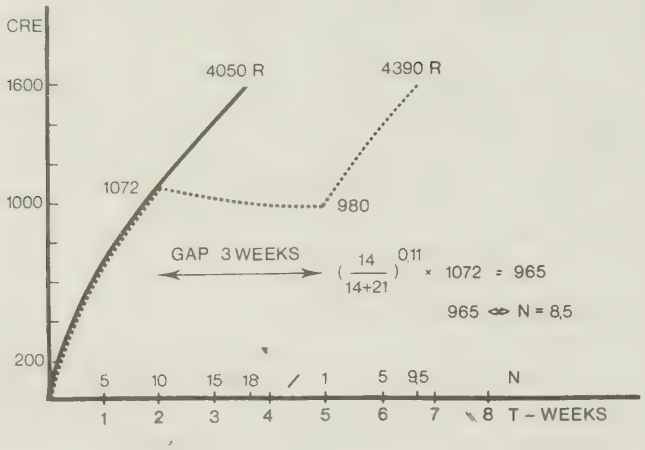


Fig. 2. Cumulative radiation effect (CRE) as a function of the number of fractions N during treatment 5 times per week without a gap and with a gap of 3 weeks after 10 fractions.

(HVL 1.2 mm Cu, exposure rate 80 R/min); the reference point for exposure is the centre of the field at the skin surface. The exposure rate at this point has been determinated by the National Institute of Radiation Protection, Stockholm. Relative exposure determinations have been performed with a Baldwin Farmer ionization chamber with half the sensitive volume lowered into a masonite phantom. To convert the exposure in R to absorbed dose in rad the f-factor 0.94 rad/R was used. Further a RBE-correction of 1.17 in relation to ^{60}Co-radiation was used in the calculations of CRE, i.e. 1 R (HVL 1.2 mm Cu) corresponds to 1.10 rad (^{60}Co). The fractionation schedule was 5×225 R per week on both fields. The two treatment schedules are presented in Fig. 1. All patients were treated identically no matter whether the patients were operated upon the left or the right side.

The intention was to administer a CRE-value of about 1 575 for each field. The number of fractions and the total dose to obtain this effect was calculated as follows (Fig. 2):

$$\text{Right field: } 1\,575 = 0.97 \times 1.10 \times 225 \times N^{0.65} \tag{1}$$

$$N = 18$$

where 0.97 approximately corresponds to $(T/N)^{-0.11}$ for 5 treatments per week. The total exposure was therefore 4 050 R and the treatment time 24 days.

Left field: The effect of the first 10 fractions within a fortnight is

$$\text{CRE (I)} = 0.97 \times 1.10 \times 225 \times 10^{0.65} \tag{2}$$

$$\text{CRE (I)} = 1\,072$$

After a gap of three weeks this value is reduced to

$$\text{CRE (II)} = \left(\frac{14}{14+21}\right)^{0,11} \times 1\,072 \tag{3}$$

$$\text{CRE (II)} = 965$$

Table 1

Mean values and total means (in per cent) of exposure measured with TLD for the 14 patients in the 'gap series' according to measurement points 1 to 6 and corresponding CRE (95 per cent confidence)

Patient No.	Measurement point					
	1	2	3	4	5	6
1	94.8±1.7	95.7±2.4	94.8±1.7	96.1±1.7	92.1±1.8	93.1±2.1
2	94.5±2.6	93.8±3.1	92.7±2.0	93.8±1.9	87.9±1.6	92.5±1.8
3	93.4±2.6	96.2±3.3	96.9±1.9	95.8±2.7	92.8±1.6	92.8±3.1
4	91.3±1.9	92.9±2.8	92.1±1.9	93.3±2.8	90.1±1.5	88.3±2.1
5	92.1±1.8	92.5±2.7	92.7±1.5	93.6±2.1	89.6±1.6	89.8±1.9
6	95.8±2.7	93.9±3.1	95.6±2.5	94.8±2.7	93.0±3.1	90.3±2.1
7	92.4±4.3	93.3±3.7	92.3±2.4	91.8±3.8	88.9±3.7	89.6±4.5
8	93.7±3.1	90.7±3.0	94.3±2.3	91.6±3.0	90.3±2.0	89.9±3.0
9	96.5±4.0	94.7±2.7	95.1±2.9	95.5±3.1	94.7±3.4	94.2±2.6
10	96.0±2.9	96.3±2.5	98.5±3.4	96.1±2.8	95.4±2.3	97.4±2.9
11	98.0±2.6	98.4±2.9	96.2±2.2	98.6±2.5	92.6±2.3	95.7±2.3
12	96.5±2.4	97.5±2.2	96.8±2.3	97.6±2.3	95.5±2.8	95.8±2.2
13	98.8±1.6	98.9±2.3	99.8±1.9	101.3±2.6	96.6±2.0	96.9±2.9
14	105.4±2.1	103.6±2.3	104.7±2.4	104.8±2.1	103.9±2.5	103.6±2.4
Total mean	95.7±2.1	95.6±1.9	95.9±2.0	96.1±2.1	93.1±2.4	93.5±2.4
CRE	1 548±20	1 549±24	1 551±20	1 557±24	1 505±20	1 515±24

Then the number of fractions equivalent to CRE (II) will be:

$$965 = 0.97 \times 1.10 \times 225 \times N^{0.65} \quad N = 8.5 \tag{4}$$

That is, CRE 965 corresponds to 8.5×225 R with 5 treatments per week. From the calculation for the right field it is known that 18 fractions give CRE 1 575 (eq. 1). Therefore after the gap on the left field $18 - 8.5 = 9.5$ fractions more are necessary. The total exposure was 4 390 R and treatment time 47 days. Thus a gap of 3 weeks has been compensated with 340 R equal to 8 per cent of the exposure.

The biologic effect of the irradiation was estimated by measuring the skin erythema and pigmentation. Both were recorded by means of a photoelectric reflexion meter (Photovolt, Model 670). An area of approximately 2.5 cm² was illuminated with light of wavelength 578 nm. Light of this wavelength is absorbed by oxyhemoglobin. The reflected light was read (in scale divisions). The increase of pigmentation resulting fom the irradiation was registered in the same manner but with light of wavelengths above 660 nm. Measurements were performed twice weekly, commencing before the first treatment, at 6 points numbered 1 to 6 (Fig. 1). In addition, the patients were photographed at least once a week.

In connection with each irradiation TLD determinations were performed including determinations at points 1 to 6 which were used for reflectance measurements

Table 2

Mean values and total means (in per cent) of exposure measured with TLD for the 10 patients in the '5 per cent series' according to measurement points 1 to 6 (95 per cent confidence)

Patient No.	Measurement point					
	1	2	3	4	5	6
1	97.7±6.1	95.5±3.2	98.8±4.7	100.0±3.1	95.6±4.0	100.1±3.0
2	100.1±2.3	101.6±3.4	98.7±3.2	100.2±2.7	96.2±2.6	98.4±3.0
3	97.8±2.8	97.0±3.2	98.1±2.8	98.4±2.7	92.6±2.8	97.8±2.6
4	97.1±4.0	95.9±3.6	98.4±3.8	97.7±3.5	92.9±4.3	97.7±2.7
5	91.9±4.3	93.9±3.2	97.3±2.7	96.8±2.6	93.9±2.8	95.9±3.2
6	94.9±1.8	96.6±3.0	94.5±2.9	97.4±2.6	92.0±2.9	94.4±3.0
7	96.1±2.2	98.8±3.2	95.8±2.1	97.4±2.1	93.4±3.0	96.4±3.0
8	94.0±3.7	97.0±5.0	97.8±2.6	98.8±3.5	96.5±3.0	98.0±3.4
9	92.9±3.5	96.9±3.0	97.7±3.6	97.3±3.5	97.0±4.6	96.3±3.5
10	91.5±3.0	96.9±3.0	94.8±3.8	98.2±3.2	93.8±3.3	94.5±3.1
Total mean	95.4±2.0	97.0±1.5	97.2±1.1	98.3±1.0	94.4±1.3	97.0±1.3

Table 3

Exposure difference, CRE and CRE difference between the two fields, calculated from the TLD determinations in Table 2 and the final exposure to each field (mean values and 95 per cent confidence)

	Measurement point					
	1	2	3	4	5	6
Exposure (R)	16 × 237	15.5 × 225 (mean)	16 × 237	15.5 × 225 (mean)	16 × 237	15.5 × 225 (mean)
Exposure diff. according to TLD (%)	6.9		7.5		5.9	
CRE	1 495±30	1 410±20	1 525±15	1 430±20	1 480±20	1 410±20
CRE difference (%)	6.0		6.6		5.0	

(LINDSKOUG 1975). The relative exposure difference between the two fields for each patient proved to be small and practically negligible (Table 1). The mean value of the average exposures for all patients was also calculated (Table 1). The daily TLD-determinations were considered as a control of the relative exposure difference between the two fields for each patient and between all the patients.

Some of the first 7 patients developed bilaterally a slightly exudative desquamation in a part of the irradiated area which healed within a week. During this period the spectrophotometer measurements were unsatisfactory. To avoid this, the exposure

Table 4

Mean values (in scale div.) of spectrophotometric measurements before irradiation for the 14 patients in the 'gap series' (95 per cent confidence)

	Measurement point					
	1	2	3	4	5	6
Erythema (reflectance)	30.2±1.6	31.8±2.3	31.9±2.4	32.9±2.8	36.4±2.2	35.7±2.3
Pigmentation (reflectance)	56.5±1.2	57.0±1.0	57.6±1.0	58.2±0.8	59.4±1.0	58.9±1.2

to the fields was reduced with 5 per cent for the following 7 patients. The mean values of the final CRE to the different measurement points, when exposure to the centre of the field is assumed to be 100 per cent (JOHNS et coll. 1952), are listed in Table 1.

The method of reflectance spectrophotometer measurements as well as the exposure control with TLD have been described and analyzed previously (TURESSON & NOTTER). In this report was also mentioned a patient treated on bilateral parasternal fields, for whom a prescribed dose difference of 5 per cent to the otherwise identically irradiated fields resulted in different skin erythema.

In order to confirm this observation 10 patients were irradiated in the right parasternal area with 5×237 R per week up to 3 790 R and in the left parasternal area with 5×225 R per week up to 3 600 R. Both areas received 16 fractions during 22 days. Thus the differences in exposure and CRE between the two fields correspond to 5 per cent. The result of the exposure controls of each patient, and the calculated mean value of the average exposures for all patients as a percentage of the exposure appear in Table 2. The last exposure to the left field was corrected according to the TLD determinations in order to achieve the required exposure difference (Table 3). For calculation of the differences in exposure and CRE (Table 3) between the two fields the relative exposures in Table 2 have been normalized to the exposure in the centre of the right field, assumed to be 100 per cent. The spectrophotometer measurements were performed at points 1 to 6 marked in Fig. 1 twice weekly.

Results

Four of the first 7 patients treated in the 'gap series' (mean CRE 1 585) developed a slightly increased skin reaction and 2 of them an initial moist-desquamation in the fields treated without gap. Two other patients developed an increased skin reaction with slight moist-desquamation on the contralateral side which was treated with gap. In one patient the skin reactions were equal on both sides.

One of the other 7 patients (mean CRE 1 520) developed an initial, slightly moist

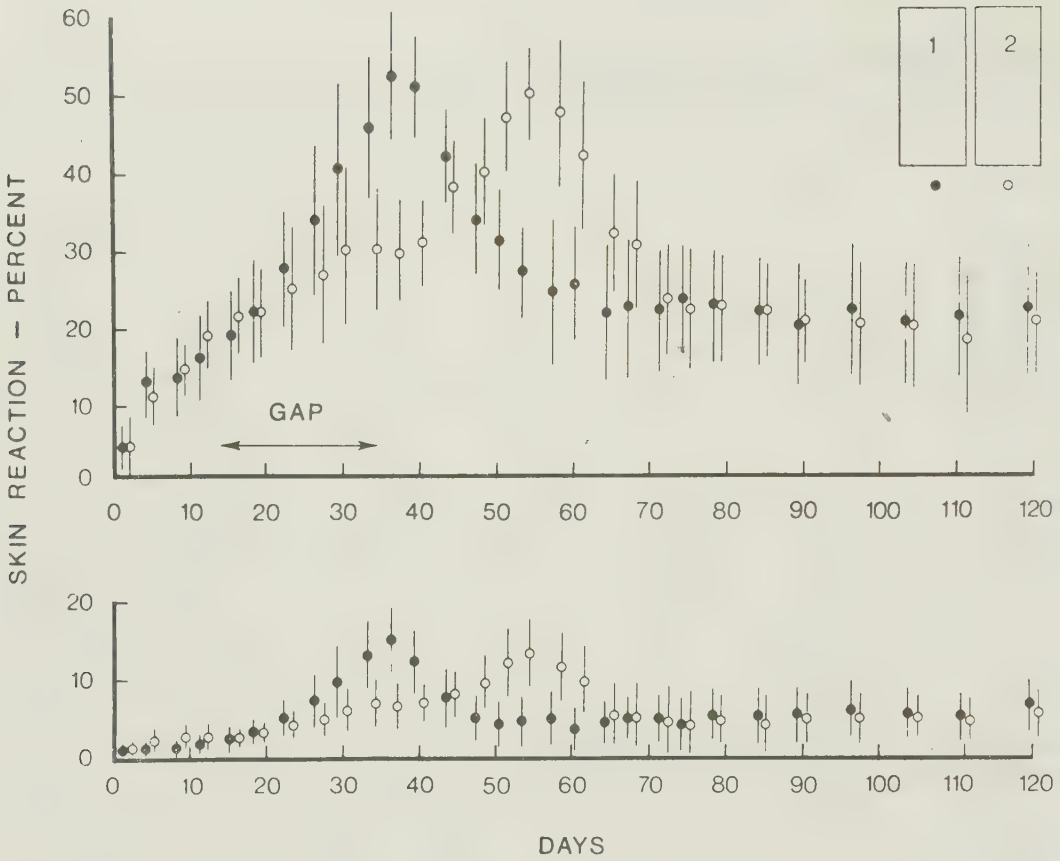


Fig. 4. Mean values of reflectance spectrophotometer measurements (per cent of pre-irradiation value) for erythema (wavelength 578 nm) and pigmentation (wavelength 660 nm) of the 14 patients in the 'gap series'. Measurement points 1 and 2 and fractionation schedules see Fig. 1 and text (95% confidence). Upper diagram: Erythema. Lower diagram: Pigmentation. ○ with gap, ● without gap.

reaction on the side treated with gap but in the others no differences in the skin reactions could be observed between the right and left sides.

The moist skin reactions in these patients were slight. They developed only in a small part of the irradiated areas and healed in all cases within a week. The maximum reactions in a patient after CRE 1 585 for each field, are illustrated in Fig. 3.

The reflectance determinations at the 6 measurement points were analyzed separately for each patient. The change in the reflectance values during the period of treatment and the follow-up was normalized to the initial values for non-irradiated skin. In Table 4 the mean values of the initial measurements for all patients are presented. The slightly increased values in the lower part of the parasternal region (points 5 and 6) are caused by the higher sympathetic tone in this region (Adams-Ray 1952).

The results of the reflectance determinations for all patients appear in Figs 4 to 6, which illustrate the development of skin erythema and pigmentation during and after

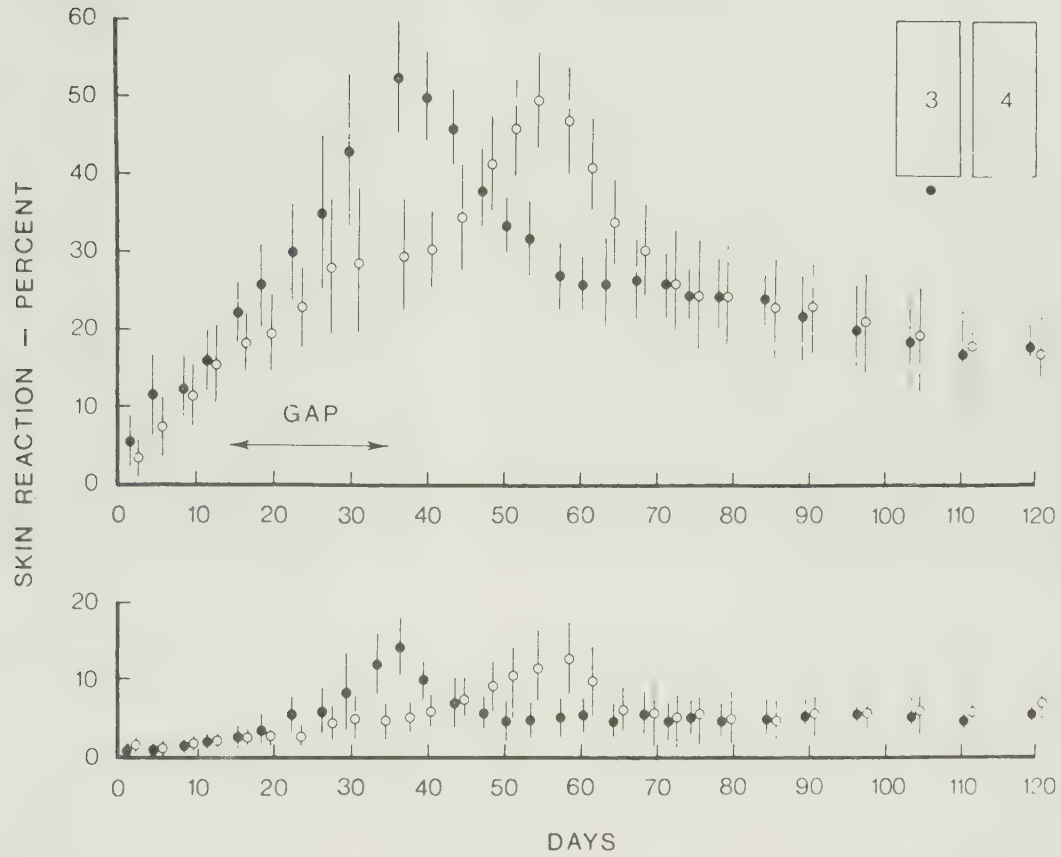


Fig. 5. Mean values of the erythema and pigmentation measurements in the middle parasternal region of the same patients as in Fig. 4. Measurement points 3 and 4. Upper diagram: Erythema. Lower diagram: Pigmentation. ○ with gap, ● without gap.

the two treatment courses. The time for maximum reactions in the different areas is given in Table 5. The maximum reaction developed somewhat earlier in the upper region as compared with the lower one, which was also noticed in the previous investigation.

Table 5

Time for maximum skin reactions in the 'gap series' after start of irradiation (mean and 95 per cent confidence)

	Measurement point					
	Right field			Left field		
	1	3	5	2	4	6
Treatment time (days)		24±1			49±1	
Erythema	38±2	39±2	41±3	54±3	55±3	55±2
Pigmentation	38±2	40±3	40±3	55±3	56±3	57±2

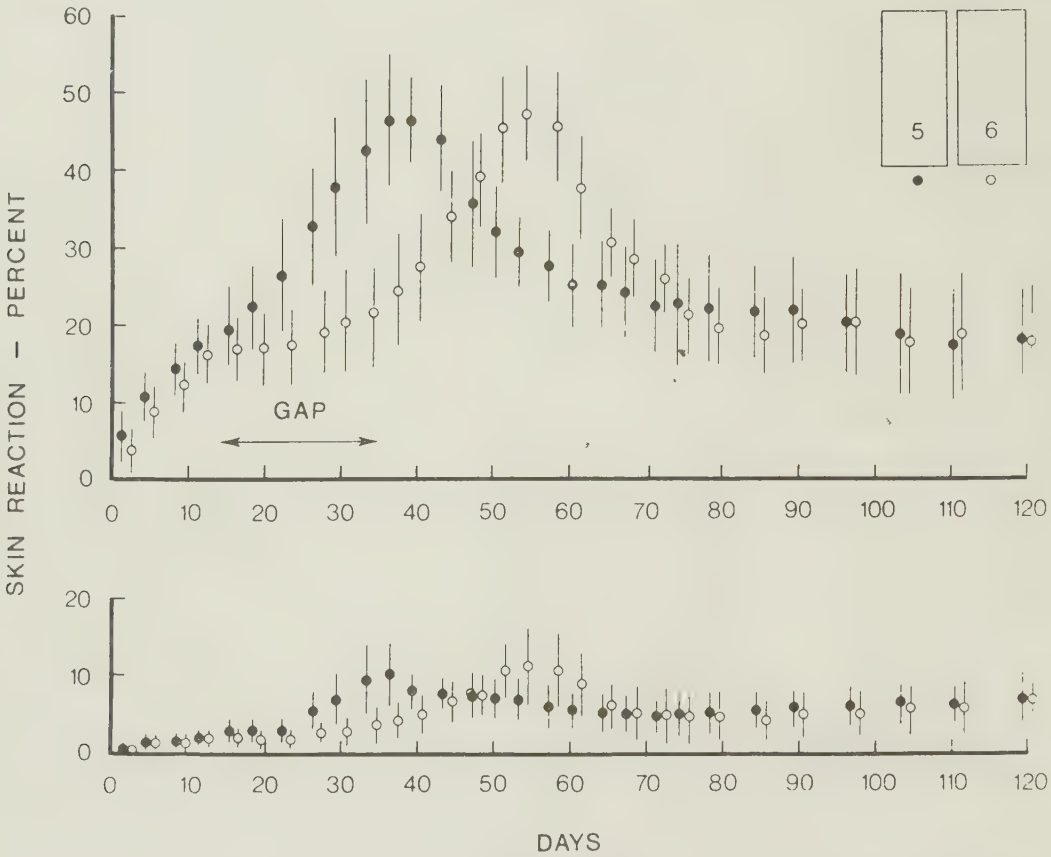


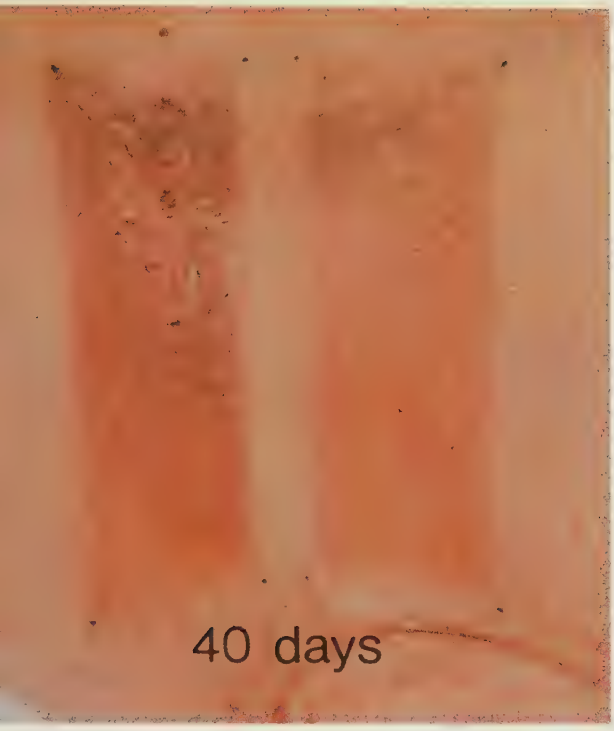
Fig. 6. Mean values of the erythema and pigmentation measurements in the lower parasternal region of the same patients as in Fig. 4. Measurement points 5 and 6. Upper diagram: Erythema. Lower diagram: Pigmentation. ○ with gap, ● without gap.

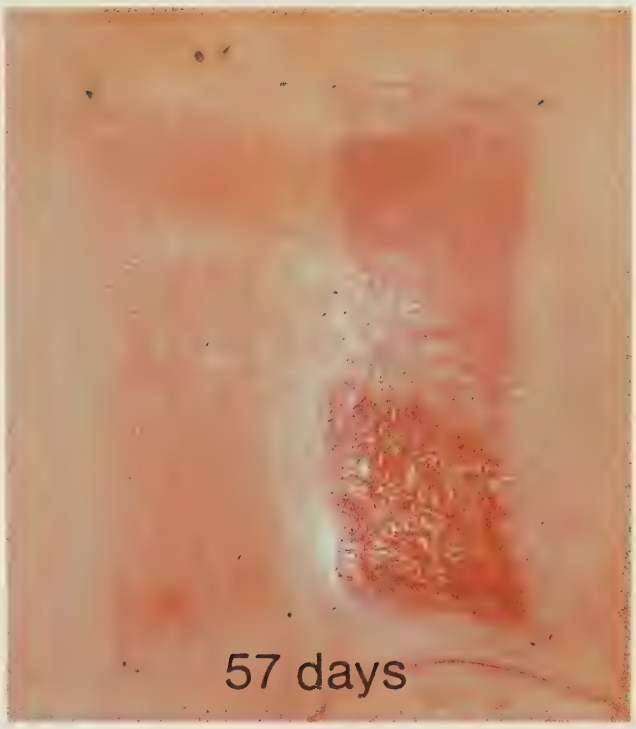
The mean values of the spectrophotometric measurements at maximum, as well as 4 days before and after the occurrence of maximum skin reaction are presented in Tables 6 and 7. They demonstrate the short duration of the maximum skin reaction and the necessity of frequent controls of the reaction after the end of the treat-

Table 6

Mean values of spectrophotometric erythema measurements in the 'gap series' at maximum, 4 days before and after maximum (95 per cent confidence)

Radiation induced erythema (% of pre-irradiation value)	Measurement point					
	1	2	3	4	5	6
4 days before maximum	47.0±5.6	46.0±5.9	48.2±5.8	46.6±5.1	43.5±5.9	43.6±4.8
Maximum	56.0±4.1	53.0±4.2	57.2±4.5	53.2±4.6	50.6±5.6	51.3±5.0
4 days after maximum	43.9±5.5	46.8±8.4	45.6±5.1	42.7±5.5	44.1±6.1	43.6±6.8





a b

ig. 3. Maximum skin reactions in a patient after CRE 1585. **a)** Right field 5×225 R per week, totally 4050 R. Left field 5×225 R per week, a gap of 3 weeks after 10 fractions, totally 4390 R.

a b

g. 7. **a)** Maximum skin reactions for both fields 2 weeks after completion of treatment, **b)** the reactions one week ter. Right field 5×237 R per week, totally 3790 R. Left field 5×225 R per week, totally 3600 R.

Table 7

Mean values of spectrophotometric pigmentation measurements in the 'gap series' at maximum, 4 days before and after maximum (95 per cent confidence)

Radiation induced pigmentation (per cent of preirradiation values)	Measurement point					
	1	2	3	4	5	6
4 days before maximum	14.6±4.4	11.2±3.6	12.9±3.6	11.0±3.9	9.6±2.7	8.9±4.5
Maximum	17.6±3.1	13.5±3.2	13.5±3.6	12.1±4.0	14.4±3.6	12.0±4.0
4 days after maximum	8.6±3.2	9.5±5.4	8.9±3.9	10.6±4.6	9.5±3.3	10.0±4.4

Table 8

Mean values of spectrophotometric measurements in the '5 per cent series' before irradiation, and at maximum reactions (95 per cent confidence). Right field: 5 × 237 R/week, totally 3 790 R/22 days (measurement points 1, 3, 5). Left field: 5 × 225 R/week, totally 3 600 R/22 days (measurement points 2, 4, 6). Time for maximum skin reactions (mean and 95 per cent confidence)

		Measurement point					
		1	2	3	4	5	6
Pre-irradiation value (reflectance in scale divisions)	Erythema	24.9±2.1	26.9±3.8	28.3±3.7	30.0±4.3	32.7±3.2	32.7±4.8
	Pigmentation	53.7±2.0	54.5±2.2	55.9±2.0	56.3±2.0	57.9±1.9	57.7±1.8
Maximum skin reaction (per cent of preirradiation value)	Erythema	48.5±3.7	42.7±7.4	49.6±5.1	46.6±4.7	46.7±6.0	40.0±7.1
	Pigmentation	16.5±3.2	15.3±3.1	15.9±3.4	15.5±3.4	13.5±4.1	11.7±3.0
Days after start of irradiation for maximum skin reaction	Erythema	36 ±2	35 ±2	37 ±2	38 ±2	39 ±2	41 ±3
	Pigmentation	37 ±3	37 ±2	38 ±3	40 ±3	40 ±2	42 ±3

ment course if the maximum is not to be overlooked. Further statistical analysis of the erythema measurements indicates that for a gap of 3 weeks a compensation of 8 per cent of the exposure applied in this schedule was adequate, except for the pigmentation in the upper parasternal region (points 1 and 2). Here the pigmentation was less marked in the 'gap treated' area.

The result from 10 patient irradiated on both parasternal fields, where the prescribed exposure difference was 5 per cent, is summarised in Table 8. By reflectance determination the effect of an exposure difference of 6 to 7 per cent could be measured to a 5 per cent significant level for skin erythema, but not for pigmentation. Visually, the difference in erythema between the fields was obvious at maximum reaction for all the patients (Fig. 7).

The mean values of the maximum reactions for all regions in the series of treatments presented in Tables 6 to 8 correlate well with the TLD determinations and with the calculated CRE values in Tables 1 to 3.

Discussion

In Tables 5 and 8 the initial reflectance determinations for non-irradiated skin over the parasternal fields are presented for both series. In the upper region the lower values correspond to a more marked light absorption due to an increased blood flow. This depends on a lower sympathetic tone in the upper region above the second intercostal space (ADAMS-RAY 1952).

Because the operation on the breast changes the innervation and blood flow in the chestwall, especially in the lower part of the parasternal region, a statistical test was performed to find out if there was any significant difference in the initial reflectance determinations between the operated and the non-operated side. This was done with a linear permutation test corresponding to the Wilcoxon one sample test (ODEN & PEHRSSON 1974).

For the patients in the 'gap series' the initial spectrophotometer measurements at 578 nm, corresponding to the maximum absorption peak of oxyhemoglobin, were significantly lower ($p < 0.05$) on the operated side compared with the nonoperated side in the middle and lower parasternal regions. This may be due to a reduction of the sympathetic innervation of the vessels by the mastectomy causing dilatation and increased blood flow. For consideration of this effect in the analysis of the result the patients were divided into left-operated and right-operated. For all patients in each group the differences in maximum reactions between the non-operated and the operated side were compared for each region. Thus the analysis was performed so that the effect of the dose compensation for gap could not be confused with the effect of the operation. The result shows a tendency to a milder maximum reaction in the 'gap field', but this was not significant.

For the patients in the '5 % series' any significant influence of the operation could not be proved for the initial spectrophotometer measurements at 578 nm.

The discrepancy found in the initial values of the non-operated and the operated side between the two series may depend on differences in operation techniques, causing different changes in blood supply of the chestwall, and on the time from operation to irradiation. As expected, the operation does not influence the initial spectrophotometer measurements of pigmentation significantly.

By reflectance determination the effect of a dose difference of 6 to 7 % could be discriminated significantly ($p < 0.05$) for skin erythema in the upper and lower parasternal region, but only almost significantly in the middle region. Thus the minimum dose difference causing measurable difference in skin erythema corresponds to 6 to 7 per cent. This is in agreement with an investigation of WAMBERSIE et coll. (1974) who demonstrated that a dose difference of 10 per cent caused a clear dif-

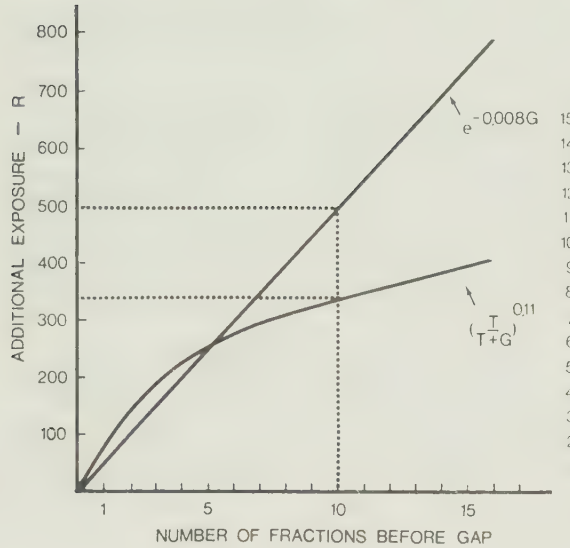


Fig. 8

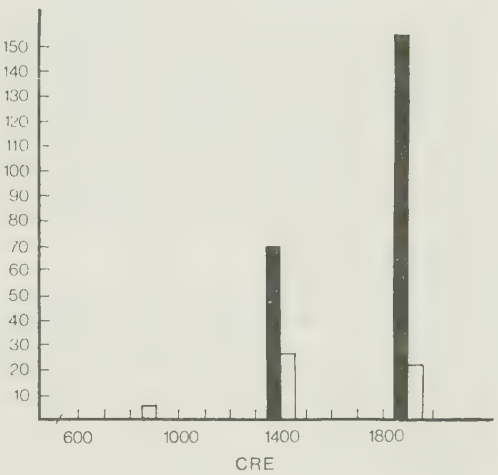


Fig. 9

Fig. 8. Depending upon the position of the gap, varying compensation for a gap of 3 weeks in a treatment course with 5×225 R per week, calculated with the corrections proposed by ELLIS and KIRK et coll. Additional exposure after N = 10 weeks. ELLIS: 340 R (8 %), totally 4 390 R. KIRK et coll.: 500 R (12 %), totally 4 550 R.

Fig. 9. The repopulation rate defined as the dose increment (rad/day) necessary to counteract repopulation of epidermal cells during the first and second week after different radiation injury expressed in CRE. ■ first, □ second week after CRE 850, 1 400 and 1 900.

ference in human skin reaction in 80 per cent of the cases, when the reactions were scored visually by a special code.

The accuracy of this investigation of ELLIS' gap correction was analysed by comparing the differences in mean values of the maximum skin reactions between each field of the 'gap series' (Tables 6, 7) and the '5 % series' (Table 8). In the latter the skin erythema was significantly different in the upper and lower region, where the exposure differences were 7 and 6 per cent, respectively. The differences between maximum reactions in the '5 % series' are evidently higher than the differences in the field with and without a gap of 3 weeks. Pigmentation is a less sensitive parameter and is not good enough for measuring the accuracy of such a small gap-correction in this case.

For the gap-correction $(T/T+G)^{0.11}$ it is evident that the duration of the gap (G days) and the treatment time (T days) before gap determine the size of the dose compensation. But from further knowledge of the CRE-formula it can be proved that the additional dose also depends on the fractionation schedule before and after gap and the definition of additional dose (KIRK, personal communication). The additional dose was defined with the presumption that after gap, treatment is resumed at the same dose per fraction as before the gap, but with a greater number of fractions and a correspondingly increased time. This definition differs from that adopted by

KIRK et coll. (1974), who compensate for a gap by increasing the dose per fraction after gap instead of the number of fractions.

The additional exposure for a gap of 3 weeks is calculated and plotted in Fig. 8 as a function of the number of fractions before gap for the fractionation schedule 5×225 R per week. These calculations may be performed with a simplified expression for the procedure described in eqs 2 to 4. The exposure compensation is then equal to $(1-(T/T+G)^{0.169}) \times D$ where D is the total exposure before gap, T and G as above. This formula is only valid when the fractionation schedule is the same before and after the gap.

In Fig. 8 also the additional exposure for a gap of 3 weeks calculated with the gap-correction $e^{-0.008G}$, is plotted as a function of the number of fractions before gap for 5×225 R per week. This gap-correction is handled in the same way as the other one described in eqs 2 to 4. The corresponding simplification for calculation of the additional exposure is $(1-e^{-0.012G}) \times D$, G and D as above.

A generalized form of the expressions is:

$$\frac{d_2}{d_1} \times \left(\frac{\varrho_1 \cdot d_1}{\varrho_2 \cdot d_2}\right)^{1.54} \times \left[1-\left(\frac{T}{T+G}\right)^{0.169}\right] \times D \qquad (5)$$

and the same for $(1-e^{-0.012G}) \times D$, where d_1 and d_2 are the dose per fraction before and after gap, and ϱ_1 and ϱ_2 are equal to $(T/N)^{-0.11}$ before and after gap.

A comparison of these functions for a gap of 3 weeks after 10 fractions indicates additional exposures of 340 R and 500 R, respectively. These compensations imply only a difference of 4 per cent in the total exposure for the required CRE value. Any difference in biologic effect of such a small exposure difference may not be discriminated by the reflectance spectrophotometer technique. For the fractionation schedule used and with a gap of 3 weeks in the treatment course before 11 fractions have been given, i.e. after a CRE value of about 1 100, both corrections may be used without any significant difference in result and there is no evidence to prefer one correction to the other.

However, the discrepancy increases between the two corrections with increasing exposure or radiation effect before the gap starts. Exposure compensation for a gap after high exposures may vary much more than after moderate exposures, because different tissues have varying potential ability to proliferate.

DENEKAMP (1973) has shown that cell-killing by irradiation induces a change in the rate of repopulation of epidermal cells in the feet of mice. By macroscopic observation of the radiation effect on skin at some specified level the proliferation rate was estimated and expressed as the dose increment (rad/day) necessary to counteract repopulation of the basal cells. Data evaluated by DENEKAMP on the repopulation during the first and second week after 4, 9 and 14 daily fractions of 350 rad (equivalent to ^{60}Co) are presented in Fig. 9. These doses correspond to CRE values 850, 1 400 and 1 900, respectively. When an appreciable amount of injury has been accumulated (CRE 1 900) the cycle time was considerably reduced (from about 5 days

to 20 hours) in order to return to the normal value when the basal cell population approaches its original size during the second week.

In marked contrast to the basal cells, the less proliferative connective and vascular tissue compartments of skin present very low proliferative response to irradiation injury. TANNOCK & HAYASHI (1972) have reported that the rate of the endothelial cell division is slow even after rather high doses of radiation. Also the split-dose experiments concerning inhibition of callus formation by HAYASHI & SUIT (1972) with gaps of 1 and 4 weeks after a single dose of 1 000 rad indicated hardly any repopulation of connective vascular tissues.

Thus for a gap late in a treatment course the dose compensation according to KIRK is probably more relevant especially for cell compartments with potentially high proliferative capacity. Where late radiation effects are concerned, the vascular injury is considered most important, therefore the gap-correction proposed by ELLIS may be more suitable.

Acknowledgements

We are very grateful to Mrs S. Benner for helping us with the spectrophotometer measurements and to the medical photographer O. Roos.

SUMMARY

In patients with mammary carcinoma, irradiated postoperatively on the parasternal regions, prospective dose calculations for different fractionation schedules have been performed with the CRE formula. The biologic radiation effect on normal tissue was recorded by reflectance spectrophotometry of skin erythema and pigmentation. The right side received 4 050 R in 25 days, the left side 4 390 R in 47 days with a gap of 3 weeks. A compensation for the gap with 8 per cent of the total exposure was found to be adequate. The smallest exposure difference that could be clearly discriminated visually and with spectrophotometry was recorded in a special series and was found to be 6 to 7 per cent.

ZUSAMMENFASSUNG

Prospektive Dosisberechungen für verschiedene Fraktionierungsschemata mit der CRE-Formel wurden bei Patienten mit einem Mammakarzinom, die postoperativ parasternal bestrahlt wurden, vorgenommen. Der biologische Strahleneffekt für Normalgewebe wurde mittels Reflektionsspektrophotometrie des Hauterythems und der Pigmentierung registriert. Die rechte Seite erhielt 4050 R in 25 Tagen, die linke 4390 R in 47 Tagen mit einem Aufenthalt von 3 Wochen. Es wurde gefunden, dass eine 8-prozentige Kompensation der Gesamtdosis für den Aufenthalt adäquat war. Die geringste Differenz in der Bestrahlung, die visuell und spektrophotometrisch eindeutig war, wurde in einer besonderen Serie undersucht; diese betrug 6 bis 7 Prozent.

RÉSUMÉ

Les auteurs ont effectué avec la formule CRE des calculs de dose prospective pour différents plans de fractionnement chez des malades atteintes de cancer du sein et soumises à une irradiation post-opératoire des régions parasternales. L'effet biologique des radiations sur le tissu normal a été mesuré par spectrophotométrie de réflectance de l'érythème cutané et de la pigmentation. Le côté droit a reçu 4 050 R en 25 jours, le côté gauche 4 390 R en 47 jours avec un intervalle de 3 semaines. Les auteurs ont trouvé qu'une compensation par 8 pour cent de l'exposition totale était convenable pour cet intervalle. Sur une série spéciale ils ont mesuré la plus petite différence d'exposition nettement décelable visuellement et par spectrophotométrie et l'ont trouvée égale à 6 à 7 pour cent.

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Control of Dose Administered Once a Week and Three Times a Day According to Schedules Calculated by the CRE Formula, Using Skin Reaction as a Biological Parameter[1]

Ingela Turesson, B.A., M.B., and Gustaf Notter, M.D.

Patients with breast cancer were irradiated postoperatively to bilateral parasternal fields. The validity of the Cumulative Radiation Effect (CRE) formula for treatment once a week and three times a day was analyzed, and both schedules were compared with treatment once a day (five times a week). The biological radiation effect on normal tissue was studied by reflectance spectrophotometry of skin erythema and pigmentation. Early skin reactions were identical after irradiation daily and once a week, respectively, but were found to be significantly more pronounced after irradiation three times a day than after treatment once a day, corresponding to an overexposure of 7–10%.

INDEX TERMS: Breast neoplasms, therapeutic radiology • Skin, effects of irradiation • Therapeutic radiology, postoperative

Radiology 120:399–404, August 1976

THE BIOLOGICAL effects of fractionated irradiation on normal tissue can easily be estimated using the umulative Radiation Effect (CRE) formula proposed by rk *et al.* (10):

$$\mathrm{CRE} = \left(\frac{T}{N}\right)^{-0.11} \cdot d \cdot N^{0.65} \qquad (1)$$

here T is the treatment time in days, N is the number of actions, and d is the dose (rads) per fraction defined for Co. We have previously employed this formula to calulate the dose to bilateral parasternal fields in patients radiated daily and twice a week following surgery for east carcinoma (15). In the same manner, studies of dose orrection for a gap of 3 weeks in a daily course of treatent have been performed. The results show that the CRE rmula is helpful in calculating biologically equivalent diation doses for use with different fractionation patterns. he biological effect was controlled by measurements of kin reactions using a reflectance spectrophotometer. sing this technique, it was possible to discriminate different degrees of skin erythema resulting from a dose fference of 6 to 7% (14). In our most recent work, we ave applied the CRE formula to two extreme fractionation chedules which have special clinical interest as an alrnative approach in treatment of poorly oxygenated tuors (2, 9)—once a week and three times a day—and ompared both of these regimens to treatment once a day.

MATERIAL AND METHODS

A total of 27 patients with breast cancer, of whom 17 ad surgery on the left side and 10 on the right, were irdiated postoperatively to bilateral parasternal fields ccording to the fractionation schedules shown in Figure Each patient in this group was irradiated daily with 235 to the right field and once a week with 675 R to the left field. A second group of 11 patients, of whom 5 had surgery on the left side and 6 on the right, were treated according to the schedules shown in Figure 2. Each patient in this group was irradiated once a day (five times a week) with 227 R to the right field and three times a day (five times a week) with 100 R to the left field, with the latter field being irradiated at about 8, 12, and 16 o'clock. In both series, fields measuring 5 × 12 cm^2 were irradiated with 200-kV x rays (h.v.l., 1.2 mm Cu; exposure rate 80 R/min.). An *f*-factor of 0.92 rad/R (12) was used to convert the exposure in roentgens to the absorbed dose in rads, and

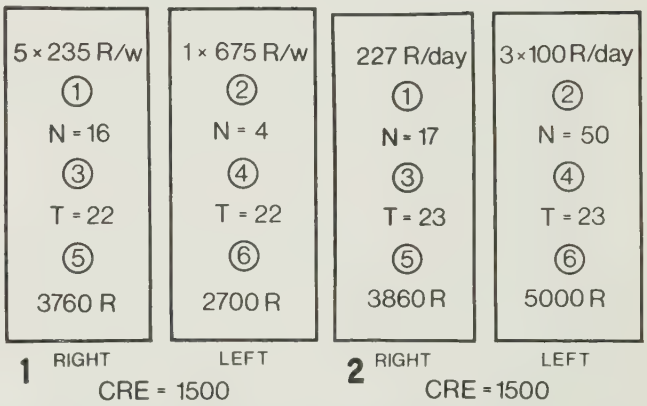

Fig. 1. Treatment schedules for bilateral irradiation of the parasternal region daily and once a week, respectively, with 200-kV x rays (h.v.l. = 1.2 mm Cu). N = number of fractions; T = treatment time in days. Reflectance spectrophotometer measurements were performed in the upper region (points 1 and 2), the middle region (points 3 and 4), and the lower region (points 5 and 6).

Fig. 2. Treatment schedules for bilateral irradiation of the parasternal region daily and three times a day, respectively, with weekly doses of 1,135 R to the right field and 1,500 R to the left field. N = number of fractions; T = treatment time in days. Reflectance spectrophotometer measurements were performed in the upper, middle, and lower regions as defined in Figure 1.

[1] From the Departments of Radiation Physics (I.T.) and Radiotherapy (G.N.), Sahlgrenska Sjukhuset, University of Gothenburg, Gothenburg, Sweden.
cepted for publication in November 1975. sjh

	Measurement Point*					
	1	2	3	4	5	6
Total Mean (%) (95% confidence level)	96.5 ± 1.8	95.7 ± 2.4	98.8 ± 1.4	98.7 ± 1.9	95.9 ± 1.3	95.7 ± 1.6
CRE (95% confidence level)	1,465 ± 25	1,455 ± 35	1,500 ± 20	1,500 ± 30	1,455 ± 20	1,455 ± 25

*Measurement points 1–6 are defined in Figure 1.

Table II: Total Mean Exposure, Corresponding CRE, and Difference in CRE Between Fields for Patients Irradiated Once a Day and Three Times a Day

	Measurement Point*					
	1	2	3	4	5	6
Total Mean (%) (95% confidence level)	93.9 ± 0.6	96.9 ± 0.5	98.0 ± 0.6	100.2 ± 1.0	97.7 ± 0.8	99.4 ± 0.9
CRE (95% confidence level)	1,435 ± 10	1,475 ± 20	1,500 ± 10	1,525 ± 15	1,495 ± 10	1,510 ± 15
(Recalculated)		(1,545 ± 20)		(1,600 ± 15)		(1,585 ± 15)
Difference in CRE (%)		2.8		1.7		1.0
(Recalculated)		(7.7)		(6.7)		(6.0)

*Measurement points 1–6 are defined in Figure 2.

Table III: Mean Preirradiation Spectrophotometric Values in Patients Treated Daily and Once a Week and Values at Time of Maximum Reaction*

	Measurement Point†					
	1	2	3	4	5	6
Preirradiation Value (reflectance in scale divisions, 95% confidence level)						
Erythema	27.6 ± 1.2	28.1 ± 1.5	28.7 ± 1.5	28.7 ± 1.6	32.7 ± 1.8	32.6 ± 2.0
Pigmentation	55.6 ± 0.8	55.5 ± 0.9	56.9 ± 0.8	57.0 ± 0.8	58.8 ± 0.9	57.8 ± 1.8
Maximum Skin Reaction (% of preirradiation value, 95% confidence level)						
Erythema	52.2 ± 2.7	52.5 ± 3.0	49.3 ± 3.5	50.4 ± 3.5	40.8 ± 4.7	41.3 ± 4.5
Pigmentation	16.2 ± 1.9	15.5 ± 1.8	15.7 ± 2.0	14.6 ± 1.7	10.8 ± 1.9	9.9 ± 1.8
Days Between Start of Irradiation and Maximum Skin Reaction						
Erythema	36 ± 1	36 ± 1	37 ± 2	38 ± 2	39 ± 2	40 ± 3
Pigmentation	36 ± 2	37 ± 2	38 ± 2	38 ± 2	41 ± 3	43 ± 4

*Right field: 5 × 235 R/week for a total of 3,760 R/22 days (measurement points 1, 3, and 5); left field: 1 × 675 R/week for a total of 2,700 R/22 days (measurement points 2, 4, and 6).
† Measurement points 1–6 are defined in Figure 1.

Table IV: Mean Preirradiation Spectrophotometric Values in Patients Treated Once a Day and Three Times a Day and Values at Time of Maximum Reaction*

	Measurement Point†					
	1	2	3	4	5	6
Preirradiation Value (reflectance in scale divisions, 95% confidence level)						
Erythema	30.7 ± 3.1	31.8 ± 3.3	32.1 ± 3.2	33.3 ± 2.9	35.2 ± 3.0	35.9 ± 3.5
Pigmentation	57.3 ± 1.4	57.3 ± 1.8	57.9 ± 1.7	58.7 ± 1.8	59.6 ± 1.4	60.0 ± 1.3
Maximum Skin Reaction (% of preirradiation value, 95% confidence level)						
Erythema	52.9 ± 3.5	57.9 ± 2.7	49.0 ± 5.1	55.4 ± 3.6	40.1 ± 6.2	49.2 ± 5.0
Pigmentation	17.2 ± 1.9	20.1 ± 2.8	14.0 ± 1.8	17.9 ± 2.4	9.1 ± 3.1	13.0 ± 4.8
Days Between Start of Irradiation and Maximum Skin Reaction						
Erythema	37 ± 2	37 ± 3	38 ± 3	38 ± 2	39 ± 4	39 ± 3
Pigmentation	37 ± 2	37 ± 2	38 ± 4	38 ± 2	40 ± 5	39 ± 3

* Right field: 5 × 227 R/week for a total of 3,860 R/23 days (measurement points 1, 3, and 5); left field: 3 × 100 R/day, 5 times a week, for a total of 5,000 R/23 days (measurement points 2, 4, and 6).
† Measurement points 1–6 are defined in Figure 2.

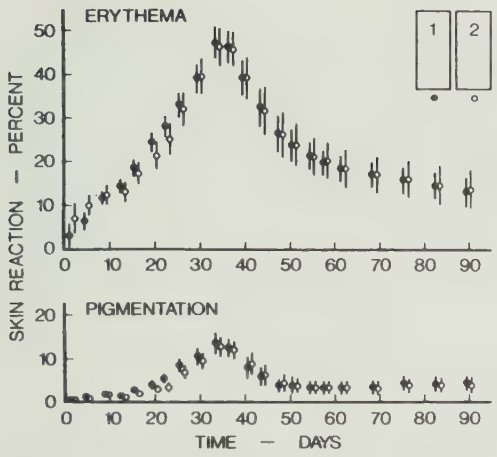

Fig. 3. Mean values of reflectance spectrophotometric measurements (percentage of preirradiation value) of erythema (wavelength, 578 nm) and pigmentation (wavelength, 660 nm) in the upper parasternal region in the 27 patients irradiated bilaterally daily and once a week, respectively. Measurement points 1 (●) and 2 (○) and fractionation schedules are shown in Figure 1 (95% confidence level).

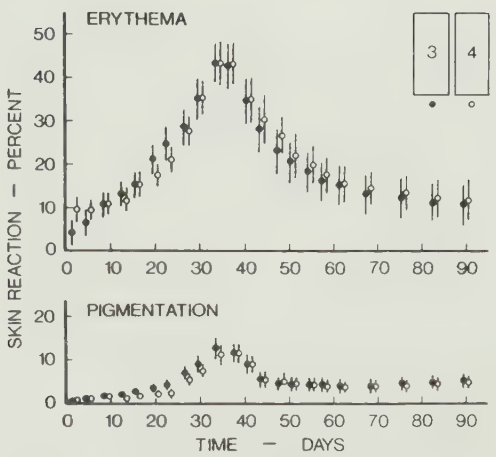

Fig. 4. Mean values of reflectance spectrophotometric measurements of erythema and pigmentation in the middle parasternal region in the 27 patients irradiated bilaterally daily and once a week, respectively. Measurement points 3 (●) and 4 (○) and fractionation schedules are shown in Figure 1 (95% confidence level).

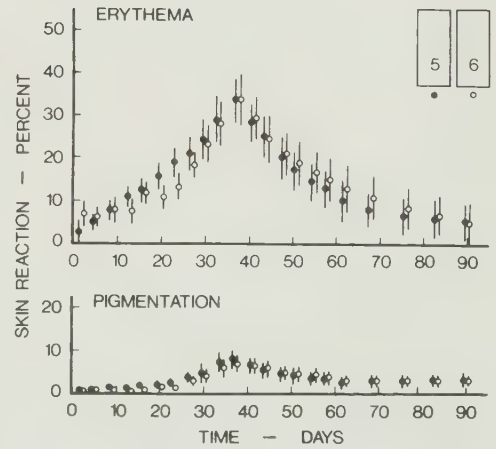

Fig. 5. Mean values of reflectance spectrophotometric measurements of erythema and pigmentation in the lower parasternal region in the 27 patients irradiated bilaterally daily and once a week, respectively. Measurement points 5 (●) and 6 (○) and fractionation schedules are shown in Figure 1 (95% confidence level).

RBE correction factor of 1.17 in relation to ^{60}Co was used calculating the CRE, *i.e.,* 1 R (h.v.l., 1.2 mm Cu) corre-onds to 1.08 rads ^{60}Co. (In our earlier investigations, an factor of 0.94 rad/R had been used.)

On the basis of the skin reactions observed in our earlier vestigations, we expected to obtain a CRE value of 1,500, rresponding to plain dry erythema. To calculate the mulative radiation effect, Equation 1 was used directly, th $(T/N)^{-0.11}$ equal to $(22/4)^{-0.11} = 0.83$ for treatment ce a week and $(23/50)^{-0.11} = 1.09$ for treatment three nes a day. Erythema and pigmentation were measured ice a week at three pairs of points (points 1–6) located the upper, middle, and lower parasternal regions (Figs. and 2) using reflectance spectrophotometry with light wavelengths 578 nm (8 nm width at half maximum) and 660 nm, corresponding to the absorption of oxyhemo-bin and melanin, respectively. Generally, each radiation eatment (but only one of the three daily sessions) was ntrolled by TLD determinations including points 1–6, ing the automated system described by Lindskoug (11). e mean total exposure for all patients, computed as a rcentage of the applied exposures, is presented for both oups of patients in TABLES I and II. The corresponding al CRE values, corrected according to the TLD deter-nations, were normalized to the exposure to the center the right field, which was assumed to be 100%. The ethod of reflectance spectrophotometry and the tech-que of exposure control with TLD have been described eviously (15).

RESULTS

The reflectance determinations at the six measurement ints were analyzed separately for each patient, and any anges during treatment or follow-up were normalized preirradiation values. The mean values of the initial re-ctance determinations (in scale divisions) for all patients are presented in TABLES III and IV. Differences between the upper, middle, and lower parasternal regions were discussed previously (14, 15). To eliminate the possibility that a change in the blood supply of the chest wall during the operation might affect the skin reaction and thus influence the statistical analysis, differences in maximum reaction between the operated and nonoperated sides in all patients were compared separately in the three parasternal regions for the groups who had surgery on the left and right side. The results of the reflectance determinations for the 27 patients treated daily and once a week are shown in Figures 3–5, which illustrate the development of skin erythema and pigmentation with the two different irradiation schedules. The time of occurrence of the maximum skin reaction and the corresponding mean spectrophotometric value are shown in TABLE III. There

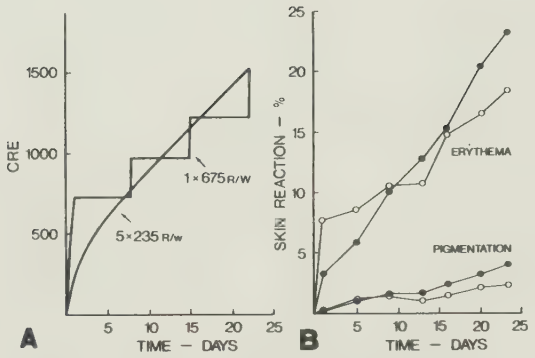

Fig. 7. A. Graphs showing the CRE during the course of treatment daily and once a week, respectively.
B. Mean skin reactions over the two parasternal fields during the treatment period. The mean value of the reflectance spectrophotometer measurements is represented by ● for points 1, 3, and 5 and O for points 2, 4, and 6.

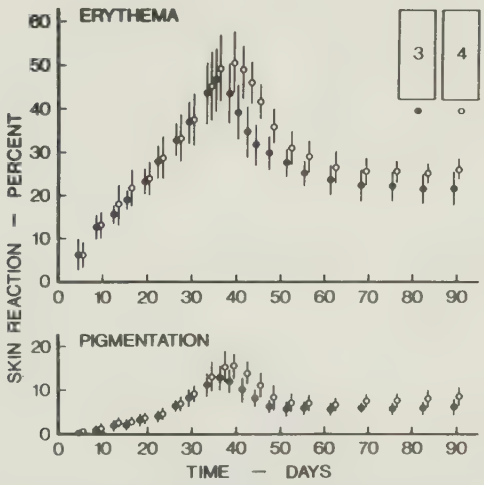

Fig. 9. Mean values of reflectance spectrophotometric measurements of erythema and pigmentation in the middle parasternal region in the 11 patients treated bilaterally once a day and three times a day, respectively. Measurement points 3 (●) and 4 (O) and fractionation schedules are shown in Figure 2 (95% confidence level).

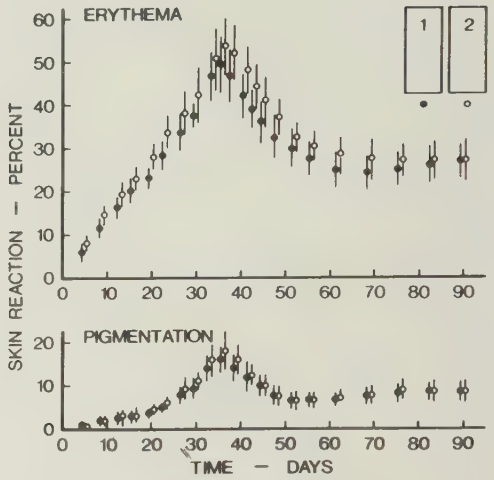

Fig. 8. Mean values of reflectance spectrophotometric measurements (percentage of preirradiation value) of erythema (wavelength, 578 nm) and pigmentation (wavelength, 660 nm) in the upper parasternal region in the 11 patients treated bilaterally once a day and three times a day, respectively. Measurement points 1 (●) and 2 (O) and fractionation schedules are shown in Figure 2 (95% confidence level).

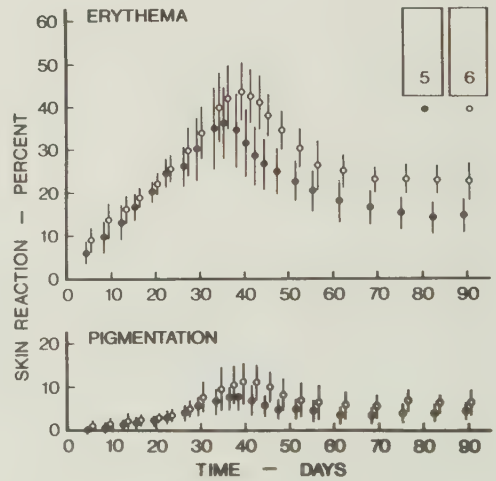

Fig. 10. Mean values of reflectance spectrophotometric measurements of erythema and pigmentation in the lower parasternal region in the 11 patients treated bilaterally once a day and three times a day, respectively. Measurement points 5 (●) and 6 (O) and fractionation schedules are shown in Figure 2 (95% confidence level).

was no significant difference between the degree of erythema or pigmentation seen in the upper region and that in the middle or lower region ($p < 0.05$), and the visual appearance was also identical on both sides (Fig. 6). However, there was a marked difference in CRE between irradiation once a week and once a day during the treatment period, and this was also reflected by the mean skin reactions over the two parasternal fields (Fig. 7).

The results of irradiation with 3 × 100 R per day compared with 1 × 227 R per day are presented in TABLE IV, showing the time of occurrence of the maximum skin reactions and the corresponding mean spectrophotometric value for all patients. The differences in maximum erythema and pigmentation between the left and right field were significant ($p < 0.05$) in all three regions. Differences in the development of erythema and pigmentation are also shown in Figures 8–10, which represent the reflectance determinations for all patients after irradiation daily and three times a day. In the left field, treated three times a day, we observed a stronger average reaction, bordering on moist desquamation (Fig. 11). Only one patient exhibited slight exudation in the upper and middle regions of the left field, and this healed within a week.

DISCUSSION

Identical acute skin reactions developed following (*a*) irradiation with 675 R once a week and (*b*) daily treatments

Fig. 6. Maximum skin reactions in a patient with a CRE of 1,500. Fractionation schedules: right field, 5 × 235 R/week for a total of 3,760 R in 22 days; left field, 1 × 675 R/week for a total of 2,700 R in 22 days.

Fig. 11. Maximum skin reactions in a patient treated bilaterally once a day and three times a day, respectively. Fractionation schedule: right field, 5 × 227 R/week for a total of 3,860 R in 23 days (CRE 1,500); left field, 3 × 100 R/day, 5 times a week for a total of 5,000 R in 23 days (CRE 1,575).

235 R. This is in contrast to the experiments with pig kin reported by Berry *et al.* (3), which showed milder early eactions after 6 large fractions given over a period of 18 ays than for daily irradiation with equivalent total doses alculated according to the NSD or CRE formula. These uthors did not find any correlation between early and late kin tolerance but felt that "skin necrosis was well pre-cted by the NSD formula." Several retrospective clinical udies indicate that the late consequences of irradiation annot necessarily be predicted from the degree of early kin reaction, due to the fact that there is a difference in ell proliferation between epidermis and vascular con-ective tissue: damage to the former is responsible for arly radiation effects, while damage to the latter is due late radiation effects (1, 4, 7). On the other hand, early d late response to fractionated irradiation of the legs of ts (6, 8) and mice (13) has been reported to show good orrelation. We felt that in radiotherapy, late tissue damage seldom observed without a corresponding early reaction, least not if standard fractionation patterns are employed, osimetry is controlled, and the tolerance levels of the ir-diated area are respected. Thus opinions differ as to the lationship between early and late tissue reactions, and e plan to systematically follow up the patients treated ily and once a week in our series for several years to find t whether the dose per fraction is of major importance the development of late radiation effects.

Irradiation with 3 × 100 R/day produced a significantly onger early reaction in the left parasternal field, com-ared with the right field which was treated with 227 R/day. om our earlier studies of skin reactions, we are able to orrelate the maximum skin reactions in the left field with a CRE value close to 1,600 (14, 15). Development of the same skin reaction in the right field would have required a daily exposure of about 240–250 R instead of the 227 R actually given. However, recalculation of the biological effect of the 3×/day schedule according to the mathematically correct use of the CRE formula for irregular treatment schedules given by Kirk *et al.* (10) gives a CRE of 1,575 (TABLE II and Appendix), assuming that repair of sublethal intracellular damage is completed within 4 hours (5, 16, 18). In this calculation the total number of fractions is grouped into 33 fractions given at 4-hour intervals and 17 fractions given at 16-hour intervals. In planning the course of treatment, we did not employ this more complicated form of calculation, as there was no experimental evidence of the superiority of this method and the results of the two calculations differed very little. However, we can now conclude that if the CRE for the 3 × 100 R/day schedule obtained by this method is indeed 1,575, which is 5% higher than the CRE calculated using the simpler technique, the accuracy of the acute reaction prediction would be enhanced. This would support the use of the more complicated calculation, since the exposure was estimated to be too high by a factor of 7–10% corresponding to the recalculated CRE difference of 6–8% (TABLE II).

According to Withers' theoretical analysis (17), the sensitizing effect of redistribution of cells throughout the division cycle between fractions becomes greatest when small doses per fraction are used. This is also favorable for dose-limiting nonproliferating tissues, which will not be sensitized by redistribution.

SUMMARY

Patients with breast cancer were irradiated postoperatively to bilateral parasternal fields. The validity of the Cumulative Radiation Effect (CRE) formula for treatment once a week and three times a day was analyzed, and both schedules were compared to treatment five times a week. The biological radiation effect on normal tissue was studied by reflectance spectrophotometry of skin erythema and pigmentation. Early skin reactions in both fields were identical in the patients treated once a week but were found to be significantly more pronounced in those irradiated three times a day, corresponding to an overexposure of 7–10%.

ACKNOWLEDGMENTS: We wish to thank our medical photographer, Ole Roos, for preparing the illustrations, and Miss Ingegerd Hermansson for helping us with the spectrophotometer measurements.

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APPENDIX

A. Direct calculation of CRE for 3 treatments per day:

$$\mathrm{CRE} = \left(\frac{23}{50}\right)^{-0.11} \cdot 1.08 \cdot 100 \cdot 50^{0.65} = 1,500$$

B. According to the permutation role proved by Kirk *et al.* (10), the irregular 3X/day schedule gives the same CRE as 33 fractions at 4-hour intervals over a period of 5.5 days followed by 17 fractions at 16-hour intervals in 17.5 days, according to the calculation

$$\mathrm{CRE}_1 = \left(\frac{5.5}{33}\right)^{-0.11} \cdot 1.08 \cdot 100 \cdot 33^{0.65} = 1,279$$

How many fractions are required for a CRE of 1,279 with 16-hour intervals between fractions?

$$1,279 = \left(\frac{17.5}{17}\right)^{-0.11} \cdot 1.08 \cdot 100 \cdot N^{0.65}$$

$$N = 44.8$$

$$\mathrm{CRE}_{\mathrm{total}} = 1.0 \cdot 1.08 \cdot 100 \cdot (44.8 + 17)^{0.65} = 1,575$$

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Prospective Studies with the CRE Formula of Prolonged Fractionation Schedules[1]

Gustaf Notter, M.D., and Ingela Turesson, M.Sc.

Different dose schedules prospectively calculated with the Cumulative Radiation Effect (CRE) formula were used for irradiation of inoperable breast carcinomas. Fractionation with 2 × 260 rad and 2 × 450 rad twice a week, and total doses corresponding to CRE levels 1900 to 2300, were compared. The results showed that prolonged fractionation increased the tolerance of normal skin and the therapeutic ratio with respect to early radiation reactions. Late reactions could not be assessed as yet because their development requires several years. With the prolonged course of treatment and 2 × 260 rad per week, no moist desquamation developed despite dose levels between 6800 and 9400 rad. Skin reactions were milder than those in the rapidly treated areas, indicating that the CRE formula cannot exactly predict acute skin reactions for very prolonged treatment schedules. The tumor regressed continuously during the irradiation schedule.

INDEX TERMS: Breast neoplasms, therapeutic radiology • Radiations, injurious effects, complications of therapeutic radiology • (Breast, effects of radiation, 0[0].470) • Treatment planning

Radiology 121:709–715, December 1976

ACCORDING to experimental and clinical observations, fractionation generally modifies the therapeutic ratio between normal and malignant tissues. Despite increasing knowledge of the influence of many different factors on the radiation effect, not enough quantitative information is available to enable calculation of the optimal relations between dose-time and fractionation for the various normal and malignant cell compartments in an irradiated target volume.

The simplest way of demonstrating the biological effect of the radiation dose with respect to fractionation has been to plot experimental or clinical data in a log-log dose-time diagram (4, 31). Isoeffect lines for biologically equivalent dose schedules for cure of squamous cell carcinoma and tolerance of normal skin compiled by Cohen (4) are presented in Figure 1. The two isoeffect lines, with the slopes 0.22 and 0.33 for cure of carcinoma and skin tolerance, respectively, cross at about 70 days, indicating that there should be a greater possibility of curing certain carcinomas without exceeding the tolerance of normal tissue if the total treatment time is prolonged beyond this point. This is naturally a simplification because the isoeffect lines are not rectilinear when more sophisticated models are used for evaluation of clinical data (5, 14, 17, 18, 20, 22, 25).

Cohen has presented a two-component model including a growth function and a volume correction with the numerical values of the parameters involved computed from clinical data. Using this model, he could calculate optimal fractionation schedules and dose levels for different malignant and normal cell populations (5, 6). For the cure of breast carcinoma, he found 6800 rad in 16 fractions over 18 days (CRE = 2160) to be an optimal dose schedule with respect to the stroma in the mammary gland (6). The interesting point is that the suggested total treatment time is considerably longer than with conventional daily fractionation.

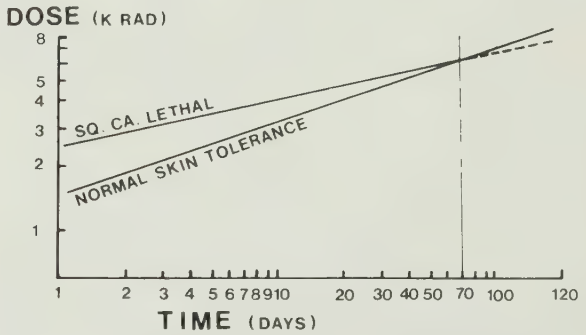

Fig. 1. Isoeffect lines for biologically equivalent dose-time schedules for the cure of squamous cell carcinoma and the tolerance of normal skin. [According to Cohen (1960), modified]

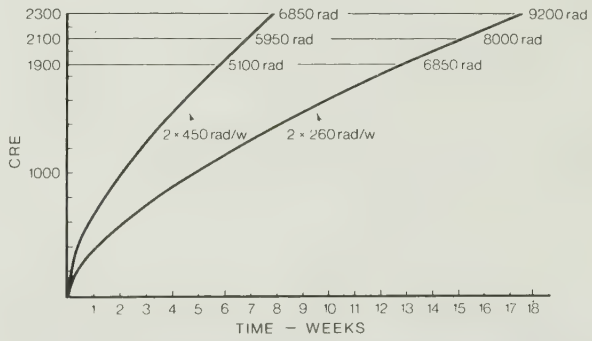

Fig. 2. Cumulative radiation effect (CRE) as a function of the treatment time during irradiation with 260 rad and 450 rad twice a week, respectively, and total tumor doses for different CRE levels used for treating inoperable breast carcinoma.

Good therapeutic results after irradiation of breast cancer patients have been observed by Baclesse (2), Fletcher (15) and ourselves, with ultrafractionation and split

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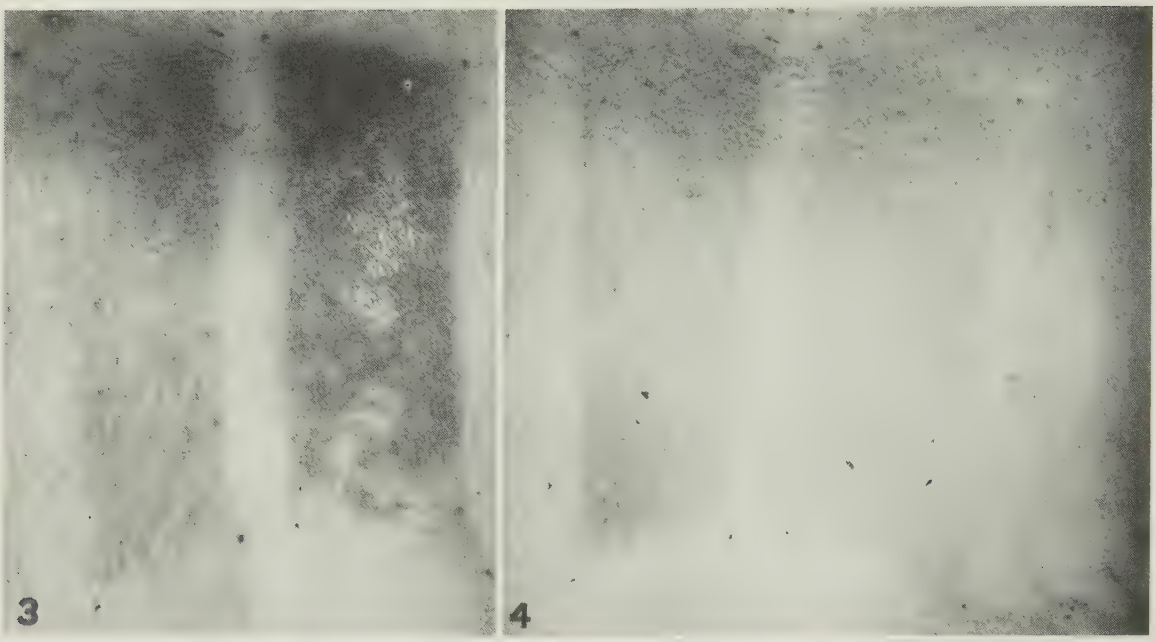


Fig. 3. Maximal skin reaction bordering on a moist desquamation in the rapidly treated left parasternal region in CASE I, 10 days after completed irradiation with 3600 R/9 fractions/30 days. The right field has received 2400 R at this time.

Fig. 4. Same case as in Figure 3. Considerably milder skin reaction is seen in the slowly treated right parasternal area at the end of the course of irradiation with 5200 R/26 fractions/90 days.

course therapy with two or three radiation series and an overall treatment time of several months.

Most breast carcinomas seem to grow slowly. A prolonged treatment time favors repopulation of more rapidly proliferating normal cells (8) and can therefore increase the therapeutic ratio, provided that the proliferation of the tumor cells is not accelerated essentially during the treatment time (21, 26). Extended irradiation also favors reoxygenation (7, 33).

It therefore seems to us to be worthwhile to study the normal tissue tolerance and the therapeutic effect on tumor cells during and after prolonged fractionation with relatively low doses per week. This paper presents early therapeutic results in some breast cancer patients who were irradiated with different fractionation schedules with use of prospectively calculated biologically equivalent radiation doses with respect to the normal connective tissue.

PATIENTS AND METHODS

Biologically equivalent radiation doses were prospectively calculated by means of the Cumulative Radiation Effect (CRE) formula according to Kirk and colleagues (23):

$$CRE = \left(\frac{T}{N}\right)^{-0.11} \cdot d \cdot N^{0.65}$$

where d is the dose per fraction in rad defined for ^{60}Co radiation, N the number of fractions and T the overall treatment time in days. The CRE formula is identical and numerically comparable with the NSD formula at the limit of normal connective tissue tolerance. The CRE formula is also defined at the subtolerance level, unlike the NSD formula. According to the CRE model, the radiation effect per fraction declines successively during the period of treatment (Fig. 2). This property of the CRE model is not valid for the NSD formula, for which the effect per fraction is considered constant and is expressed as partial tolerance, *P. T.* The two models are therefore not comparable at the subtolerance level.

The reliability of the CRE formula in radiotherapy for total treatment times up to 50 days has previously been demonstrated by us (34–36). For extremely prolonged courses of treatment, however, we had no experience with the CRE formula as regards early and late skin reactions. A pilot study was therefore performed on a patient operated upon for breast cancer for comparison of the early radiation reaction in normal skin after courses of irradiation with total treatment times of 30 and 90 days, respectively (CASE I). The patient was treated postoperatively (with 200 kV x rays, h.v.l. 1.2 mm Cu, exposure rate 80 R/min, field size 5 × 12 cm^2) on the right parasternal region with 200 R twice a week, 26 fractions during 90 days, totaling 5200 R, and on the left field with 400 R twice a week, 9 fractions during 30 days, totaling 3600 R. The two schedules correspond to CRE values of 1560 and 1580, respectively, if the f-factor 0.92 rad/R and an RBE-correction of 1.17 in relation to ^{60}Co are used in the CRE calculations. Skin erythema was studied twice a week by reflectance spectrophotometric measurements at wavelength 578 nm (34).

In order to investigate the radiation effect of a prolonged

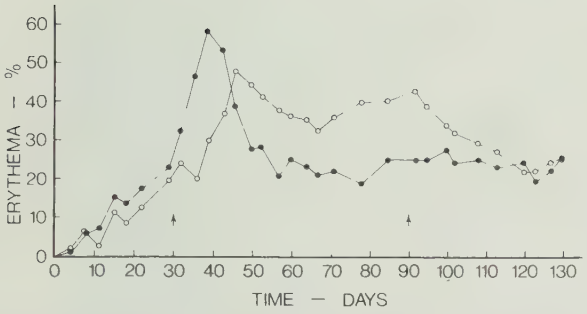


Fig. 5. Reflectance spectrophotometric measurements (% of preirradiation value) for erythema (wave-length 578 nm) of CASE I treated with the following exposures:
2 × 400 R/week, 9 fractions in 30 days, totaling 3600 R.
2 × 200 R/week, 26 fractions in 90 days, totaling 5200 R.

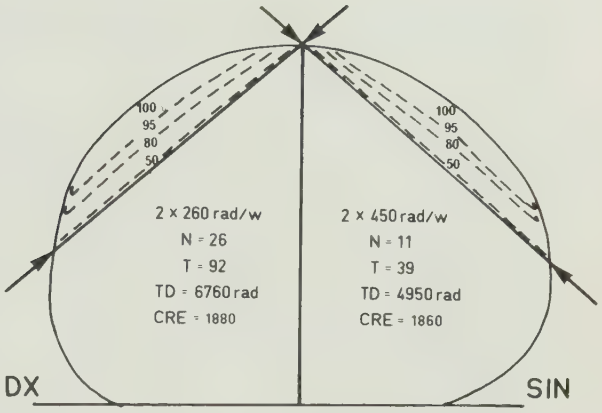


Fig. 6. Treatment plan, fractionation schedules and dose levels for bilateral tangential irradiation of the chest wall by ^{60}Co for CASE II.

reatment schedule, not only in normal but also in tumor ssue, and to study the therapeutic ratio, patients with ilateral breast cancer were irradiated with different ractionation schedules on the right and left side. In patients vith unilateral carcinoma, the target volume was divided nto two halves which were treated differently. The patients vere irradiated with 450 rad and 260 rad twice a week with ^{0}Co (CASES II and III). In other patients with tumors unuitable for division of the treatment target, the breast and xilla were irradiated in *one* large volume with 260 rad wice a week.

The total doses were calculated to be biologically quivalent using the CRE formula. Figure 2 shows how the RE increases during the course of treatment fractionated vith 260 rad and 450 rad twice a week. The diagram also ives the total doses required for the CRE levels 1900, 100 and 2300 which we have applied for the treatment f breast carcinomas. The individual dose schedules used n the patients described in this article will be given toether with the results of the treatment.

RESULTS

In the patient who was irradiated in order to test the eliability of the CRE formula for a very prolonged treatment me, a strong erythema bordering on a moist desquamaon developed in the rapidly treated left parasternal region 3600 R/9 fractions, 30 days) with a maximum 8–13 days fter completion of irradiation (Fig. 3). On the right side, vhich was irradiated during 90 days with approximately alf the dose per week but a 45% higher total dose (5200 /26 fractions, 90 days), a much milder skin reaction deeloped (Fig. 4).

The skin erythema during and after each course of iradiation, measured by reflectance spectrophotometry and xpressed as per cent of the preirradiation value, is shown Figure 5. In the rapidly treated field, the skin reaction was tronger than in the slowly treated one and reached its naximum 40 days after commencement of irradiation. In he slowly treated area, the first maximum reaction was ecorded 50 days after commencement of treatment and ecreased slightly thereafter despite further irradiation. A new broader maximum of almost the same degree as the first one was observed at about 90 days, at the completion of irradiation.

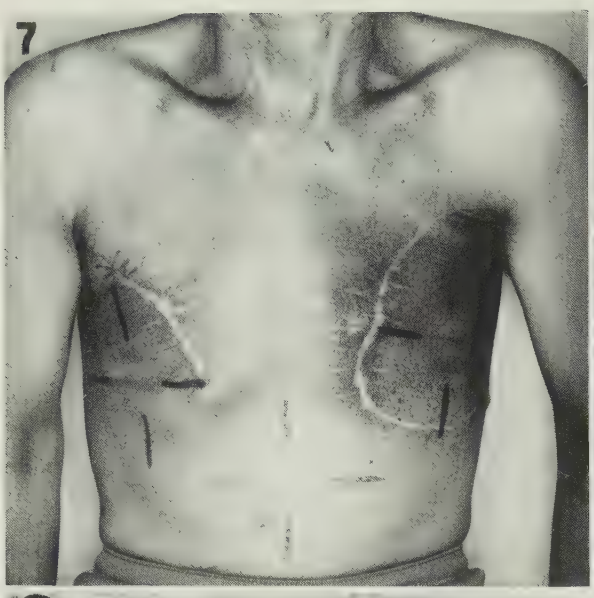
The first of the tumor patients (CASE II, Figures 6–9) was operated upon for bilateral breast carcinomas and after some years, subcutaneous metastases developed in the chest wall, mainly on the right side. Both sides of the chest wall were irradiated simultaneously by ^{60}Co with two tangential fields. The fractionation schedules and dose levels applied are described in Figure 6.

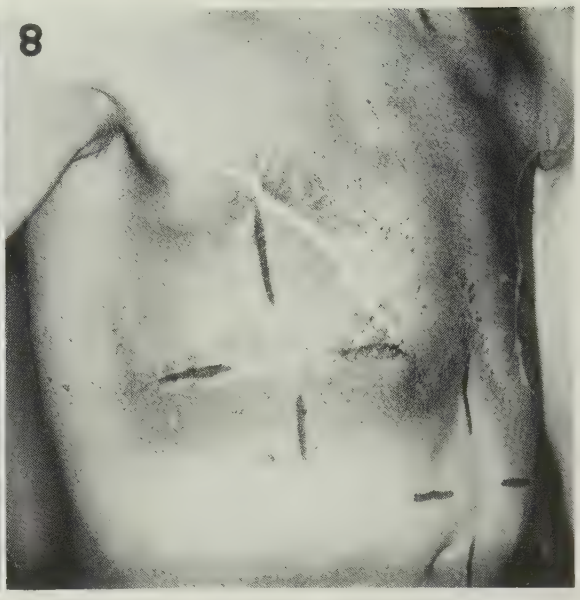
Figure 7 shows the skin reaction in the chest wall on the 49th day after the start and 10 days after completion of irradiation. On the rapidly treated left side, the reaction reached its maximum at this time. On the slowly irradiated right side, only a mild pigmentation was visible at this time. A stronger reaction did not develop until about 70 days with a maximum at 92 days, on completion of the irradiation course (Fig. 8). One year after irradiation, no difference could be observed between the right and left sides of the chest wall as regards the condition of the soft tissues (Fig. 9).

The second tumor patient (CASE III, Figs. 10–13) suffered from an inoperable, low, differentiated ductal carcinoma (Fig. 10). The treatment volume of the primary tumor was divided into two halves, each of which was irradiated with two opposite tangential fields.

The upper half of the breast was treated twice a week with 450 rad, 13.2 fractions within 42 days and a total dose of 5950 rad. The lower area received 260 rad twice a week, 30.8 fractions within 104 days and a total dose of 8000 rad. Both dose schedules correspond to CRE 2100.

Maximal skin reaction in the upper treatment area developed about two weeks after completion of irradiation, with moist desquamation in almost the whole area. In the lower part only a slight pigmentation developed in the normal tissue around the tumor at this time after 4680 rad. The tumor itself had shrunk and become necrotic in both the rapidly and the slowly treated areas despite the considerable difference in the doses applied.





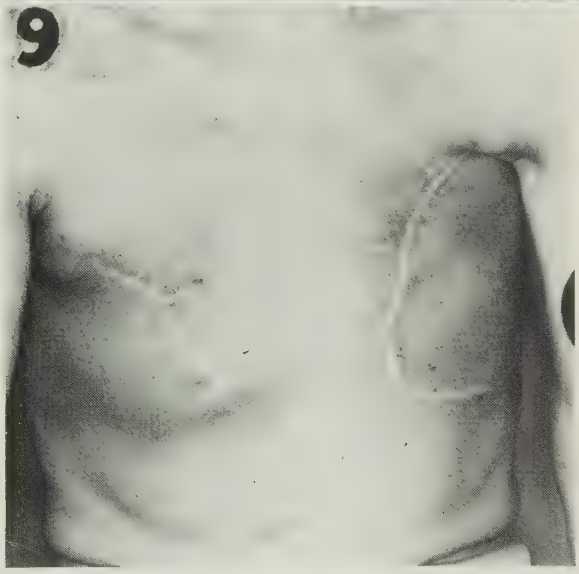


Fig. 7. Maximal skin reaction in CASE II on the rapidly treated left side 10 days after completion of irradiation with 4950 rad/11 fractions/39 days. The right side has received 3640 rad at this time.

Fig. 8. Same patient as in Figure 7. Maximal skin reaction is seen on the slowly irradiated right side at completion of the treatment with 6760 rad/26 fractions/92 days.

Fig. 9. Same patient as in Figure 7, one year after irradiation.

Re-epithelialization in the upper area starts very soon as may be seen in Figure 11 which was taken one month after completion of irradiation. This demonstrates the good healing potential of the skin after irradiation with a dose corresponding to CRE 2100. There is no exudative dermatitis in the lower area at this time.

Two months after completion of irradiation in the upper area, the moist desquamation had disappeared almost totally and telangiectases and depigmentation started to develop. In the lower area the irradiation had just been completed at this time (104 days). No moist desquamation and only slight pigmentation was visible in the normal skin. The tumor tissue, however, had become totally necrotic in both treatment areas.

Forty-five and 105 days, respectively, after completion of irradiation, only a small superficial ulcer remained in the center of the upper and lower area (Fig. 12). It disappeared during the following three months leaving an unpigmented scar in the center of the earlier tumor area (Fig. 13). Depigmentation and telangiectasia had increased in the upper area and differed clearly from the slight pigmentation in the slowly irradiated lower area.

DISCUSSION

For the prospective calculation of biologically equivalent doses, the CRE formula according to Kirk and colleagues (23) has been used. The CRE concerns subtolerance or tolerance only for normal connective tissue, which, however, usually represents the upper limit of the radiation dose which can be used in clinical radiotherapy. Since the CRE makes us independent of the number and size of fractions, the interval between fractions and the total dose, we consider the formula to be a simple and useful guide in routine clinical use for expressing the biological effect we wish to apply to the target (27, 29).

We have investigated the reliability of the formula for total treatment times of between 22 and 50 days, 4–50

Fig. 10. Inoperable ductal carcinoma of CASE III in the entire right breast and lower axilla. Treatment volume is divided into an upper and lower half of equal size for irradiation with different dose schedules.

Fig. 11. CASE III, one month after completion of irradiation in the upper area with 5950 rad/13.2 fractions/42 days. The lower area has now received 5720 rad/22 fractions/73 days.

Fig. 12. CASE III, 45 and 105 days, respectively, after irradiation.

Fig. 13. CASE III. There is complete disappearance of the tumor 170 and 230 days, respectively, after irradiation.

ractions, and doses per fraction between 110 and 730 rad, n a comparison of conventional daily treatment with nce-a-week, twice-a-week and three-times-a-day chedules, and a course of treatment including an interval f three weeks (34–36). In these clinical investigations, ve found the validity of the formula concerning early skin rythema and pigmentation to be very good. The late re-ctions cannot yet be assessed because their development enerally takes several years.

As we had no experience of the reliability of the CRE ormula for very prolonged irradiation, we compared such reatment with a shorter treatment course in a patient by ilateral irradiation of the parasternal region with prospectively calculated biologically equivalent dose. We found in this pilot study, by reflectance spectrophotometer measurements and also by visual examination, that the early skin reaction in the slowly treated area was milder than in the rapidly treated one (Figs. 3, 4 and 5). This is probably due to the relatively rapid proliferation of the basal cells and perhaps also to stimulation of the proliferative capacity in this cell compartment (8) which is favored by a prolonged radiation course. Hence, it is obvious that the CRE formula cannot exactly predict acute skin reactions for very prolonged treatment schedules.

This was also confirmed by the irradiation of other patients with inoperable breast carcinomas treated by similar

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THE RESPONSE OF PIG SKIN TO SINGLE AND FRACTIONATED HIGH DOSE-RATE AND CONTINUOUS LOW DOSE-RATE ^{137}Cs-IRRADIATION

INGELA TURESSON and G. NOTTER

INTRODUCTION

The CRE-system introduced by Kirk and his colleagues (36, 37, 38) includes formulae for fractionated high dose-rate irradiation and continuous low dose-rate irradiation, which allow calculation of the cumulative radiation effect, CRE, on normal tissue for varying dose schedules and irradiation techniques.

For fractionated high dose-rate irradiation the formula is:

$$CRE_F = \left(\frac{T}{N}\right)^{-0.11} \cdot d \cdot N^{0.65} \qquad (1)$$

where d is the absorbed dose per fraction, N the number of fractions and T the overall treatment time in days.

For continuous low dose-rate irradiation with constant dose rate throughout the period of treatment, the formula is

$$CRE_C = k \cdot D \cdot T^{-0.29} \qquad (2)$$

where D is the total absorbed dose and T the total irradiation time in days. k is a normalizing constant to ensure equivalent radiobiological effects for the same value of CRE given either with fractionated high dose-rate irradiation or continuous low dose-rate irradiation. Kirk and colleagues (38) proposed a value of 0.77 for this factor, but it was later changed to 0.80 (39).

The formula for continuous irradiation can also be written in another form:

$$CRE_C = k \cdot r \cdot T^{0.71} \qquad (3)$$

where r is the dose rate expressed as the dose[x)] per day, k and T as above.

The validity of the CRE_F-formula for fractionated irradiation has been determined by us for acute skin reactions in prospective clinical investigations and has been reported elsewhere (60,61,62). The reliability was found to be better than 7 % when daily irradiation five times a week was compared with irradiation twice a week, once a week, and 3 times a day.

The experiments presented in this paper were performed to find out the total doses required for equivalent normal tissue reactions caused by single and multifraction doses of irradiation applied at a dose rate of 1.48 Gy/min and continuous irradiation at a dose rate of 1.20 Gy/hr. Pig skin was chosen as normal tissue in this case. Dose-effect curves were therefore established for the early and medium-term response of pig skin to these different irradiation strategies from which we determined:

1) the relative biological effectiveness (RBE) between single doses applied at high and low dose rate, and

2) the correspondence of the CRE_F and CRE_C-formulae, i.e. the normalizing constant.

The value of the normalizing factor in the CRE_C-formula was determined on the following two assumptions:

a) the CRE_F-model is a good predictor of the total dose required for equal biological effects for different fractionated dose schedules,

b) the time-exponent minus 0.29 or plus 0.71 is correct.

x) dose means absorbed dose throughout this paper

The first assumption is based on our own clinical data. The second assumption implies that the CRE_C-model per se is correct in relating the total dose required for equal effects for different irradiation times or dose rates. The formula can be used for this purpose without knowing the value of k. The time-exponent in the CRE_C-model was based on clinical data for human skin from Ellis (14) and Paterson (53). Mitchell (48) has also reported iso-effect doses over a wide range of treatment times. Experimental studies on pig skin performed by Atkins and coll. (2) indicated a value of minus 0.30 for this exponent. The different sets of data are shown in Figure 1.

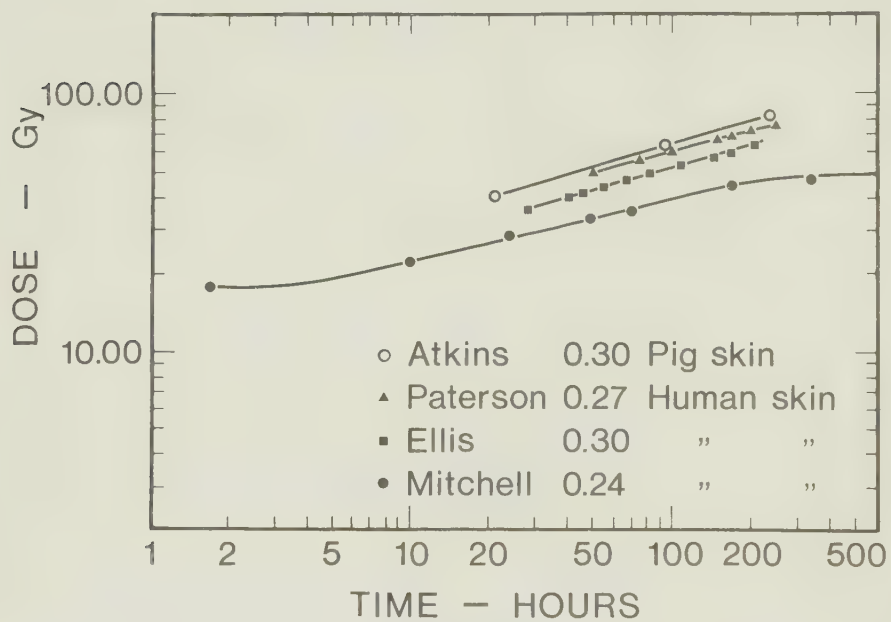

Figure 1. Iso-effect lines for skin reactions to continuous irradiation at different dose rates. The numerical values refer to the slope of the time-dose relationship reported by different authors (Modified from Atkins et al (2)).

The aim of our investigation and experimental design was to elucidate the question of which is the biologically most suitable irradiation mode for intracavitary and interstitial therapy: fractionated high dose-rate or continuous low dose-rate irradiation? This question is of topical interest to radiotherapists owing to the increasing use of afterloading techniques.

Continuous irradiation at different low dose rates also offers an alternative to multifractionation regimes at high dose rates for selecting optimal dose-time distributions in external radiotherapy of malignant tumours.

However, as a frame-work it is necessary to evaluate the difference between the effects of high and low dose-rate irradiation as regards the tolerance of normal tissue which is the limiting factor in clinical applications, and to find models for calculating the total dose for a constant risk of complications with either technique. Only with this knowledge, and with well-established and documented dose distributions is it possible to investigate seriously what type of fractionated high dose-rate or continuous low dose-rate irradiation will give the best therapeutic effect.

METHODS AND MATERIALS

Radiation sources

In order to investigate the correspondence between the CRE_F and CRE_C - formulae for calculation of the biological effect of high dose-rate and low dose-rate irradiation, two plane ^{137}Cs-sources with activities of 444 GBq and 4.6 GBq were used (applied by the Radiochemical Centre, Amersham). The β - irradiation was filtered with stainless steel. The high-activity source was placed in a specially constructed head of lead and was controlled from outside the treatment room. The low-activity source was fixed during irradiation in an applicator of aluminium, allowing rotation of the source without its being taken out of the applicator. A few millimetres above the surface of the skin to be irradiated, a sheet of 1 mm polystyrene was placed, to eliminate very soft radiation without reducing the air supply to the skin. A stretched net prevented the skin bending towards the source during irradiation (Fig. 2).

Dosimetry

The aim of the dosimetric measurements was to establish:

1) the absorbed dose distribution in one plane parallel to the active surface of the sources,
2) the dose rate at the surface and at a depth of 10 mm,
3) the depth-dose distribution for both sources.

All dosimetry measurements refer to the geometry and set-up used in the treatment position at a given time.

The absorbed dose distribution at a depth of 0.5 mm in a polystyrene phantom measured with film dosimetry is presented in Figure 3. The homogeneity at the high dose-rate source was good. The activity of the low dose-rate source was inhomogeneously distributed, giving poor field flatness. However, an ac-

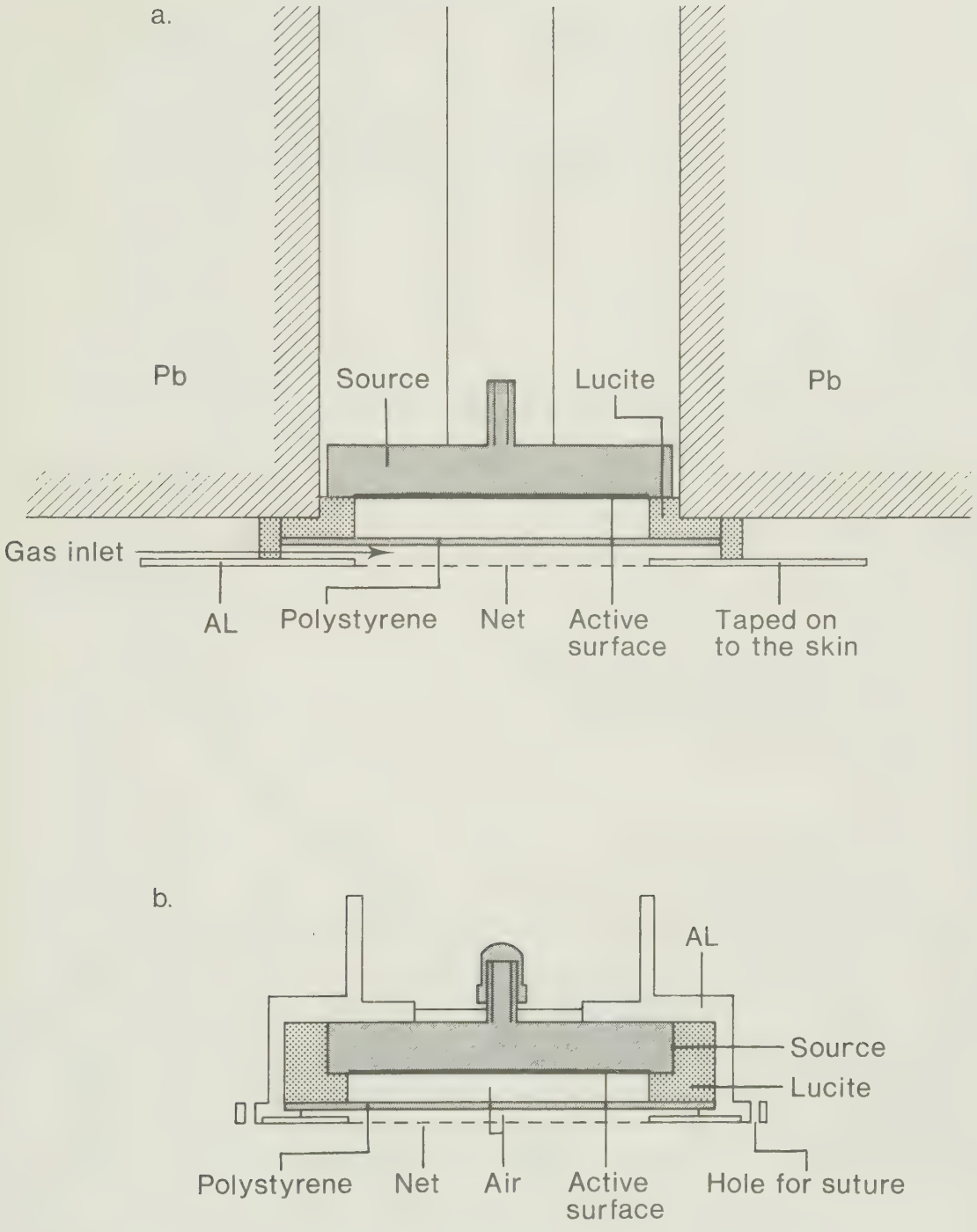

Figure 2. Cross-sections of the ^{137}Cs-irradiators showing the position of the sources relative to the skin surface during irradiation. a) high-activity source, b) low-activity source.

ceptable homogeneity could be obtained with a 180^{o} rotation of the source after half the irradiation time. All applications with the low dose-rate source therefore required this rotation procedure, which resulted in the homogeneity shown in Figure 3. The 90 % isodose was 30 mm in diameter for both sources. SSD was 10 mm and 7 mm for the high and low dose-rate source respectively.

Quantitative determinations of the dose rate at the surface and at a depth of 10 mm in a polystyrene phantom were carried out with TL-dosimetry, a Farmer ionization chamber and a liquid ionization chamber. Absorbed dose-rate measurements were performed with LiF (7)-teflon dosemeters in discs of 0.13 mm thickness (0.031 g cm^{-2}) with a diameter of 2 and 3 mm. The TL-dosemeters were individually calibrated in a ^{60}Co radiation therapy beam (SSD 75 cm). In a group used for a measurement series at least five of the dosemeters were left for calibration in order to correct for variations in sensitivity between repeated utilizations. All the dosemeters in the group were subjected to exactly the same heating and cooling procedure in each measurement series. The dosemeters were read out on a Harshaw 2000 TLD system.

The TLD measurement procedure may include a significant systematic error due to a non-uniform dose distribution within the dosemeter; a problem which in the present study may be accentuated by the fact that the calibrations were performed with a radiation quality different from that used in measurements and due to interface effects associated with the difference in atomic composition between the dosemeter and the medium. This phenomenon has been elucidated by Bertilsson (6) and Rudén and Bengtsson (56). To eliminate this effect the mean absorbed dose at each measurement depth was expressed as the mean value of two identical series of measurement at the same depth. Only the read-out orientation of the dosemeters differed between the two series. The difference between the two read-out directions was found to be 5 % at the surface of the phantom and increased to about 10 % at depths greater than 10 mm. A higher reading was found with the entrance side turned towards the light detector during the read-out.

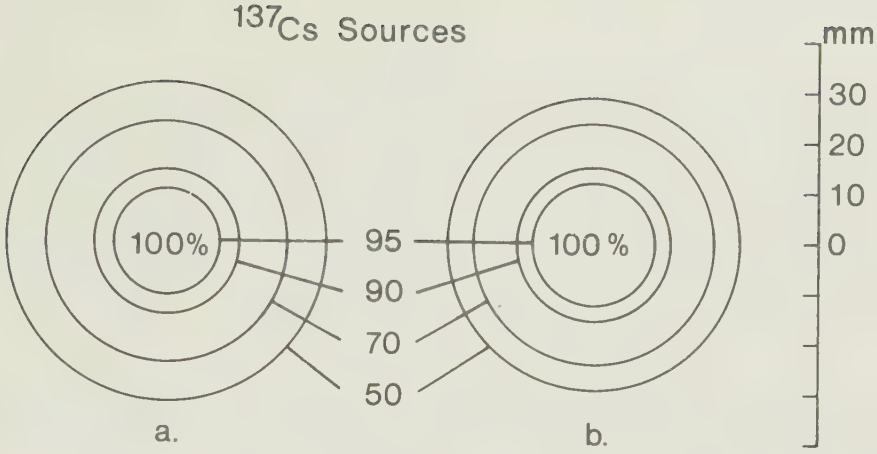

Figure 3. Field flatness at 0.5 mm depth in a polystyrene phantom a) high dose-rate source, b) low dose-rate source.

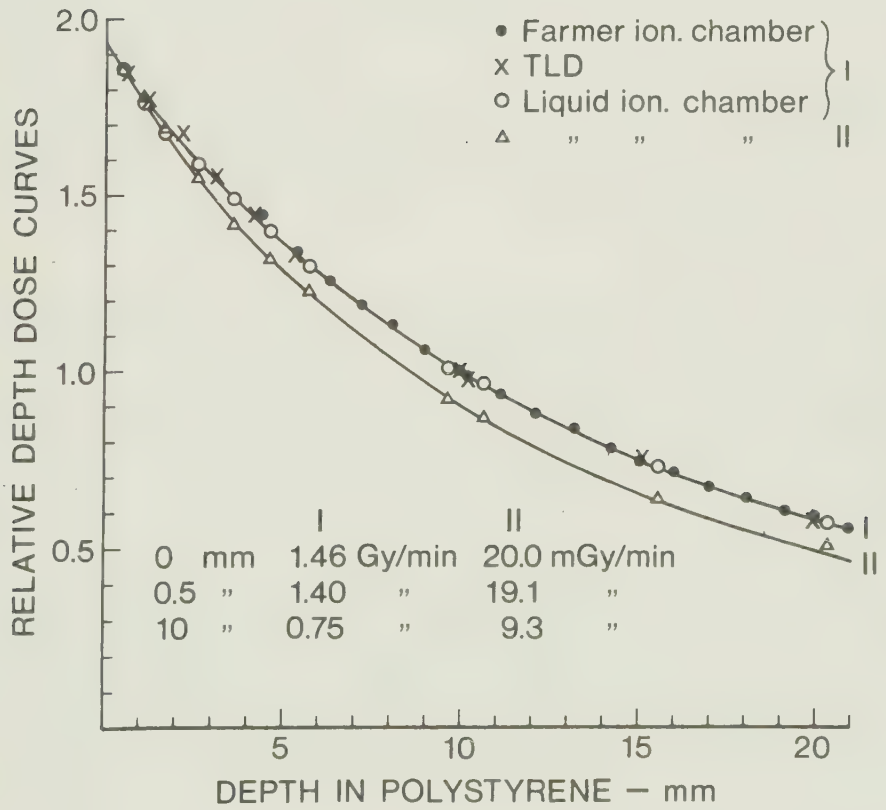

Figure 4. Relative depth-dose distribution for the high dose-rate source (I) and low dose-rate source (II) at SSD of 10 and 7 mm, respectively, measured with different detectors, and dose rates at 0, 0.5 and 10 mm.

The surface dose, here defined as the dose to the TL-dosemeter placed at the surface of a polystyrene phantom in the centre of the field, was found to be 1.48 ± 0.027 (S.D.) Gy/min and 20.0 ± 0.49 (S.D.) mGy/min for the high and low dose-rate source respectively. No correction for decay was applied over the experimental period, which lasted about six months.

Quantitative determinations of the dose rate at a depth of 10 mm were performed with TLD and a calibrated Farmer ionization chamber independently of each other. The symmetry axis of the cylindrical air ionization chamber with a volume of 0.2 cm^3 represents the effective measurement point (47). A liquid ionization chamber (65) with a sensitive area of 3 mm in diameter was calibrated towards the air chamber at the depth of 10 mm, which made it possible to determine the dose rate of both sources at a depth of 0.5 mm. The absorbed dose rates at a depth of 10 and 0.5 mm are given together with extrapolated values at 0 mm in Figure 4. The ratio of the dose rates at 0.5 mm between the two sources, found to be 73 with the liquid ionization chamber, showed good agreement with the same ratio at the surface (74 with TL-dosimetry).

The depth-dose distribution for the high dose-rate source was determined with TL-dosimetry from the surface to a depth of 20 mm and was checked at depths equal to or greater than 4.4 mm with the air chamber. The depth doses were also confirmed with the liquid ionization chamber. For all the detector systems employed here, the depth-dose measurements were normalized to the response at the depth of 10 mm. The depth-dose curve for the low dose-rate source could be determined quite conveniently with the liquid ionization chamber. The measurements were normalized to the response at a depth of 0.5 mm, which made it possible to compare the depth-dose distribution between the two sources presented in Figure 4.

Animals

The skin of immature female and castrated male domestic pigs from a Yorkshire x Swedish Landrace crossbred stock was used for these experiments. The weight of the pigs varied between 25 and 40 kg when the experiment started and increased by 10 to 20 % over the period of irradiation.

The pigs were irradiated with the high dose-rate source under anaesthesia induced by breathing oxygen with halothane through a face mask and maintained by repeated intravenous injections of thiopentone sodium (Pentothal-sodium, Abott) into the ear vein at intervals of about five minutes. The pig could be anaesthetised for at least two hours in this way. The ambient temperature was $26.5^{o} \pm 1.5^{o}$ (maximum deviation) and oxygen was gassed over the skin during the treatment in order to counterbalance any reduction of the oxygen supply to the skin due to the anaesthesia.

The low dose-rate irradiations were performed without anaesthesia and with the source fixed in the applicator sewn onto the skin. The ambient temperature was $21^{o} \pm 1^{o}$.

The centre of every field was marked by an indian ink tattoo, to enable as exact an application of repeated dose fractions as possible. The tattoo also guided the exact application when minimal radiation effects developed and after fading of more pronounced reactions, caused by fractionated as well as single doses.

All doses quoted refer to the dose in the centre of the field. The fields were spaced with a distance of at least 12 cm between their centres.

Dose schedules - Pilot study

In a pilot study on two pigs the following dose schedules were applied:

Pig I, High dose rate: 60.0 Gy in 10 fractions over 29 days, CRE_F = 23.8 to five fields on the left side of the pig. Furthermore, two fields were given single doses of 23.0 Gy and one 31.0 Gy.
Low dose rate: 30.0 Gy in 25 h, CRE_C = 23.7 (k = 0.80), to five fields on the right side.

Pig J, High dose rate: 63.6 Gy in 10 fractions over 28 days, CRE_F = 25.3 to five fields on the right side of the pig. One field was treated with a single dose of 31.0 Gy.
Low dose rate: 33.0 Gy in 27.5 h, CRE_C = 25.3 (k = 0.80) and successively increasing doses of 38.4 Gy in 32.0 h, 45.0 Gy in 37.5 h, 48.4 Gy in 40.3 h, and 55.3 Gy in 46.1 h. Each dose level was given to two fields on the left side of the pig.

As the results from these two pigs revealed that the dose levels for continuous irradiation predicted by the CRE_C-formula produced a significantly less pronounced effect than the corresponding dose levels for equal CRE_F-value, it became necessary to establish dose-effect relationships for the different irradiation techniques.

Dose schedule - Main study

In the main experiment five pigs were irradiated, 2 of them (Pigs N and P) with single doses of high and low dose rate and the other 3 (Pigs Q, R and S) with both single and fractionated doses to the following dose levels:

High dose rate: single doses between 22 and 34 Gy and/or 7 to 8 fractions of 7 to 11 Gy each, every four days.

Low dose rate: single doses between 40 and 80 Gy. The exact treatment schedules employed in these pigs are presented together with the results.

The type of fractionation for the high dose-rate irradiation was chosen for the following practical and scientific reasons.

a) To avoid the toxicity of too frequent anaesthesia within two hours and the sometimes very difficult intravenous injections in the ears of the animal owing to the limited number of veins available.

b) A fractionation interval of 90 to 100 h allowed the continuous irradiations to be performed in parallel with the fractionated irradiation course.

c) So far, radiotherapists using after-loading techniques with high-activity sources instead of radium implants practice a few large dose fractions spaced over several weeks.

d) From the radiobiological point of view, we considered that the type of fractionation regime chosen was not critical, because we have a good deal of clinical experience of different fractionation schedules. Taking account of the small field size used on the pigs the dose per fraction and treatment time falls well within the range in which the CRE_F-formula was clinically investigated. (We will revert to this point in the discussion.)

Whenever possible the doses given (in 100 %) were confirmed by TL-dosimetry. All fractionated irradiations were measured. As the dosemeters for each field were applied before the first field was treated and were not taken off until all fields had been irradiated at each session, the dose contributions from the surrounding fields were included in the dose measurements.

Skin reaction scoring system

The skin reaction was scored at least three times a week according to an arbitrary scale presented in Table 1. Interpolations were carried out between the

Table 1 Scoring system for early-term and medium-term skin reaction in the pig.

1.0	slight erythema
2.0	erythema
3.0	marked erythema
	moist desquamation
	or necrosis with
3.5	Ø < 10 mm
4.0	10 ≤ Ø ≤ 15 "
4.5	15 < Ø < 25 "
5.0	Ø ≥ 25 "

defined levels. The reflectance spectrophotometer method used in the clinical investigations (61) was also tried, but later abandoned because the measurements were difficult to evaluate when moist desquamation or necrosis developed. The scoring system also provided the most sensitive method of detecting differences in erythema of the pig skin.

Figure 5 shows the development of the skin reactions (in score units) plotted against time after commencement of irradiation in a pig after fractionated and continuous irradiation at three different dose levels. Skin reactions after single doses at two dose levels with high dose rate given to the same pig are also shown in the lower graph of this Figure. In the most typical curves showing development of skin reactions two dose-dependent waves can be distinguished; an early-term reaction and somewhat later a "medium-term reaction". The early reaction, which came up very fast, appeared about 25 to 30 days after commencement of the fractionated irradiation and often several days earlier after single doses, and was characterized by erythema and/or moist desquamation of varying degree. The acute reaction varied considerably in duration. Sometimes a moist desquamation healed very rapidly. In other cases healing was prolonged and the reaction proceeded to a second wave, the medium-term reaction, without having the acute reaction completely healed.

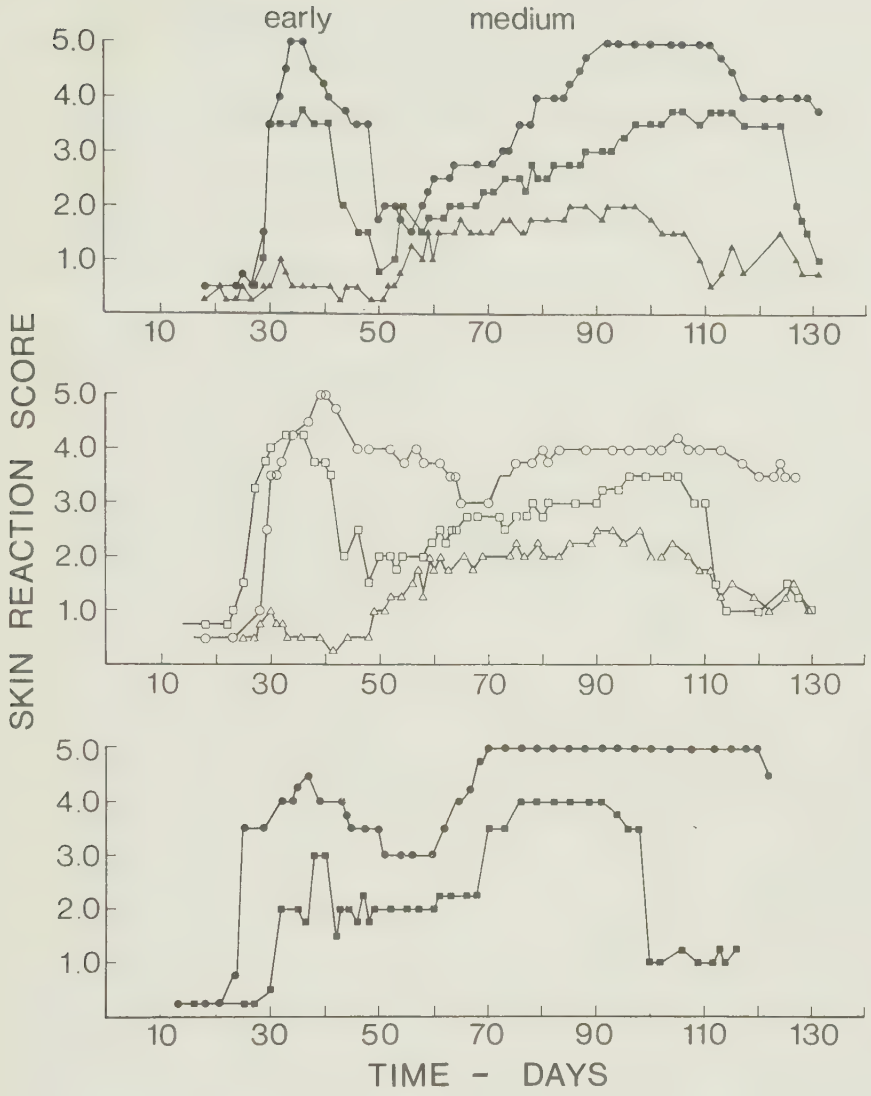

Figure 5. Development of the skin reactions after commencement of irradiation:
upper graph: fractionated doses - high dose rate
middle " : single doses - low dose rate
lower " : single doses - high dose rate
Pig Q, fields: ● 2 sin, ■ 3 sin, ▲ 4 sin, ○ 2 dx, □ 3 dx, △ 4 dx, ● 1 sin, ■ 1 dx (see table 4).

The medium-term reaction is characterized by erythema or necrosis depending on the dose levels. When the erythema progressed to necrosis there was usually a shift in colour from red to pale indigo before the ulcer became apparent. This type of reaction was given a score of 2.5 or 3, depending on the degree.

The radiation effects to the skin were expressed as the average skin reactions, which were calculated simply by measuring the area under each curve between appropriate time limits and dividing the areas by this time interval.

The early-term reaction for each field was averaged over a 20-day period from the point of time when the reaction reached 30 % of the peak reaction, and dose-response curves were constructed.

In order to construct dose-effect curves for the medium-term reaction, the second wave of each field was averaged over a time interval of 55 days, which in each pig was the same for all fields irradiated with single as well as fractionated doses, except that the interval for fractionated irradiated fields was chosen 10 days later than for single doses. However, the time interval was somewhat shifted from pig to pig, depending on the evolution of the second-wave reaction. Dose-effect curves were also constructed in respect of both the early and the medium-term reaction, including the scoring period between the first- and second-wave reaction.

Determination of RBE and normalizing constant

The relative biological effectiveness, RBE, of single doses with low dose-rate (reference) and high dose-rate irradiation was determined from the dose-response curves as the ratio between doses of low dose-rate and of high dose-rate irradiation required to produce the same degree of average skin reaction.

The normalizing constant was determined in a similar way from the dose-effect curves for fractionated and continuous irradiation. The $CRE_{F(x)}$-value was calculated for the total fractionated dose required for a certain effect level (x), and the total dose, D_x, required with continuous irradiation for the same effect (x) was determined and the irradiation time, T_x, was calculated for D_x given with the dose rate of 28.8 Gy/day. The value of k was obtained from the equation:

$$CRE_{F(x)} = k \cdot D_x \cdot T_x^{-0.29} \qquad (4)$$

RESULTS

The pilot pigs. The skin reactions after fractionated and continuous irradiation of Pig I were so slight that they could not be evaluated with good precision. However, a significantly lower effect after continuous irradiation could be distinguished, expressed as a very early regrowth of hair after the low dose-rate irradiation compared to the fields that had received fractionated irradiation, which were still epilated about 8 weeks after completion of treatment. At this time additional single test doses of 31.0 Gy and 23.0 Gy with the high dose rate were given to 8 of 10 fields previously exposed to fractionated and continuous irradiation, 4 fields with each dose level, in order to estimate the difference in skin damage produced by these different irradiation techniques.

The early skin reactions were still very slight in all fields, but a medium-term reaction (60 - 100 days) developed after 31.0 Gy to the continuous low dose-rate fields which became almost as pronounced as the medium-term reaction that developed after 23.0 Gy to the fractionated high dose-rate fields (Fig. 6). Thus, the effect difference corresponds to about 8 Gy given with the high dose rate. As was found for the pigs N, P and Q (to be demonstrated later) the RBE of the low relative to the high dose-rate irradiation is 2.35, when considered the medium-term reaction. According to this fact 8 Gy with high dose rate is equivalent to 18.8 Gy (8 x 2.35) with low dose rate. When 18.8 Gy is added to the 30.0 Gy given previously the total dose is 48.8 Gy with low dose rate. This dose level would approximately correspond to the fractionated dose given (60.0 Gy in 10 fractions over 29 days). The value of the normalizing constant, k, then becomes 0.57 instead of 0.80.

The average skin reaction after single doses with the high dose rate (23.0 Gy and 31.0 Gy) in this pig agreed well with the reactions of other pigs investigated later.

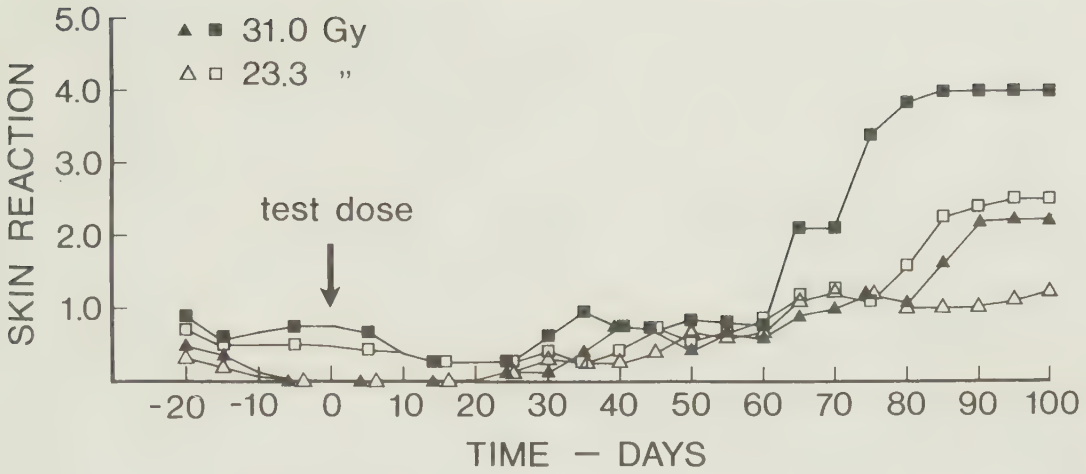

Figure 6. Development of the skin reactions in Pig I after additional single test doses of 31.0 and 23.3 Gy at high dose rate:

■□ fields earlier irradiated with a fractionated high dose-rate regime

▲△ fields earlier irradiated with a continuous low dose-rate regime.

Each symbol represents the mean value of two fields.

The average medium-term reaction of Pig J at different dose levels, calculated over 40 - 95 days for single doses with high and low dose rate and over 50 - 105 days for fractionated irradiation are presented in Figure 7. According to the CRE_C-model, the average reaction to 33.0 Gy, given with continuous low dose-rate irradiation (indicated by the filled triangle), should be equal to the average reaction of the fractionated dose (the open square) but was in fact found to be significantly less pronounced. This also indicates that the continuous dose predicted by the formula with a value of 0.80 of the normalizing constant was too low. From the dose-response curve, it was determined that a continuous dose of 51.8 Gy instead of 33.0 Gy was required for equating the effect of the fractionated dose. The normalizing constant, k, then becomes 0.58 at the average medium-term reaction of 1.53. If both the early and medium-term reactions were considered, only extrapolation of the data could give a value of k approximately equal to 0.50. It may also be concluded that the RBE was greater than 1.8 for this pig.

Determination of RBE - Main study

The total single doses of high and low dose rates given to Pigs N, P and Q are presented in Tables 2, 3 and 4 x) together with the total average reaction (early + medium-term) for Pigs N and Q calculated between 20 and 105 days and for Pig P between 20 and 110 days after irradiation, and the average medium-term reaction only estimated between 50 and 105 days for Pigs N and Q and between 55 and 110 days for Pig P. The evaluation of the average early-term reaction was described above. Figure 8 shows the dose-effect data achieved by each irradiation regime fitted to a straight line for these pigs. The regression equations for these lines, which describe the average skin reaction as a function of dose, are summarized in Table 7. x) The RBE values were derived from the ratio of protracted and acute single doses calculated from these equations for the average reaction 1.5, 2.5 and 3.5. The mean RBE values were found to be 1.97 for the early-term reaction, 2.35 for the medium-term reaction and 2.26 for early + medium-term reaction. The RBE values, summarized in Table 8, for early-term and medium-term reactions differ significantly

x) presented in appendix

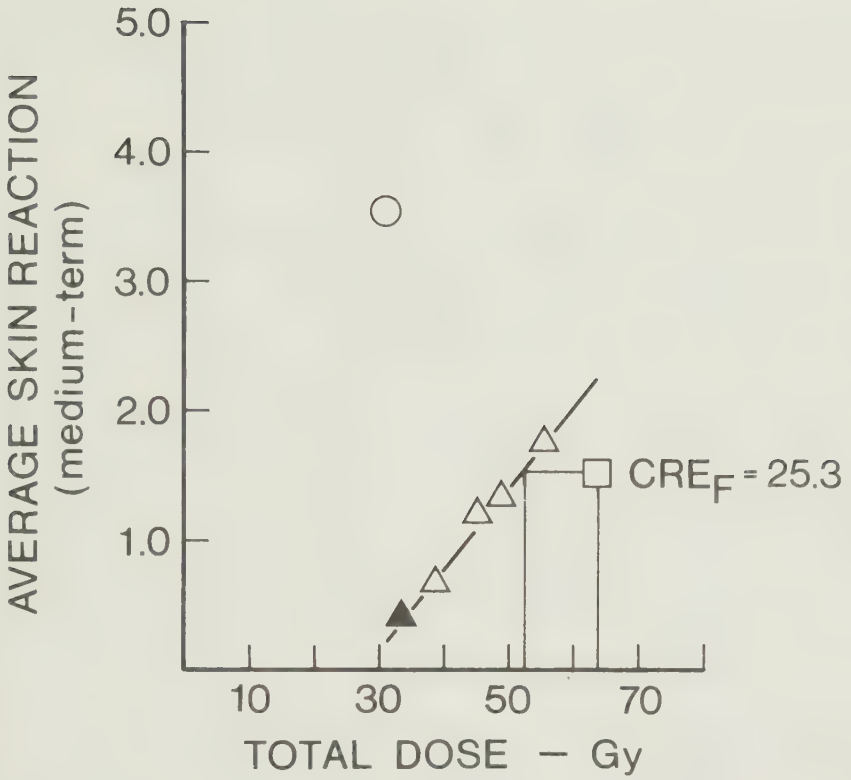

Figure 7. Average medium-term reactions of Pig J after

○ single dose at high dose rate, one field,

□ fractionated high dose-rate regime, mean value of five fields,

△ continuous low dose-rate irradiation, mean value of two fields,

▲ dose predicted by the CRE_C-formula, see text.

The continuous dose-effect data were fitted to the regression line: $Y = 0.061x - 1.63$.

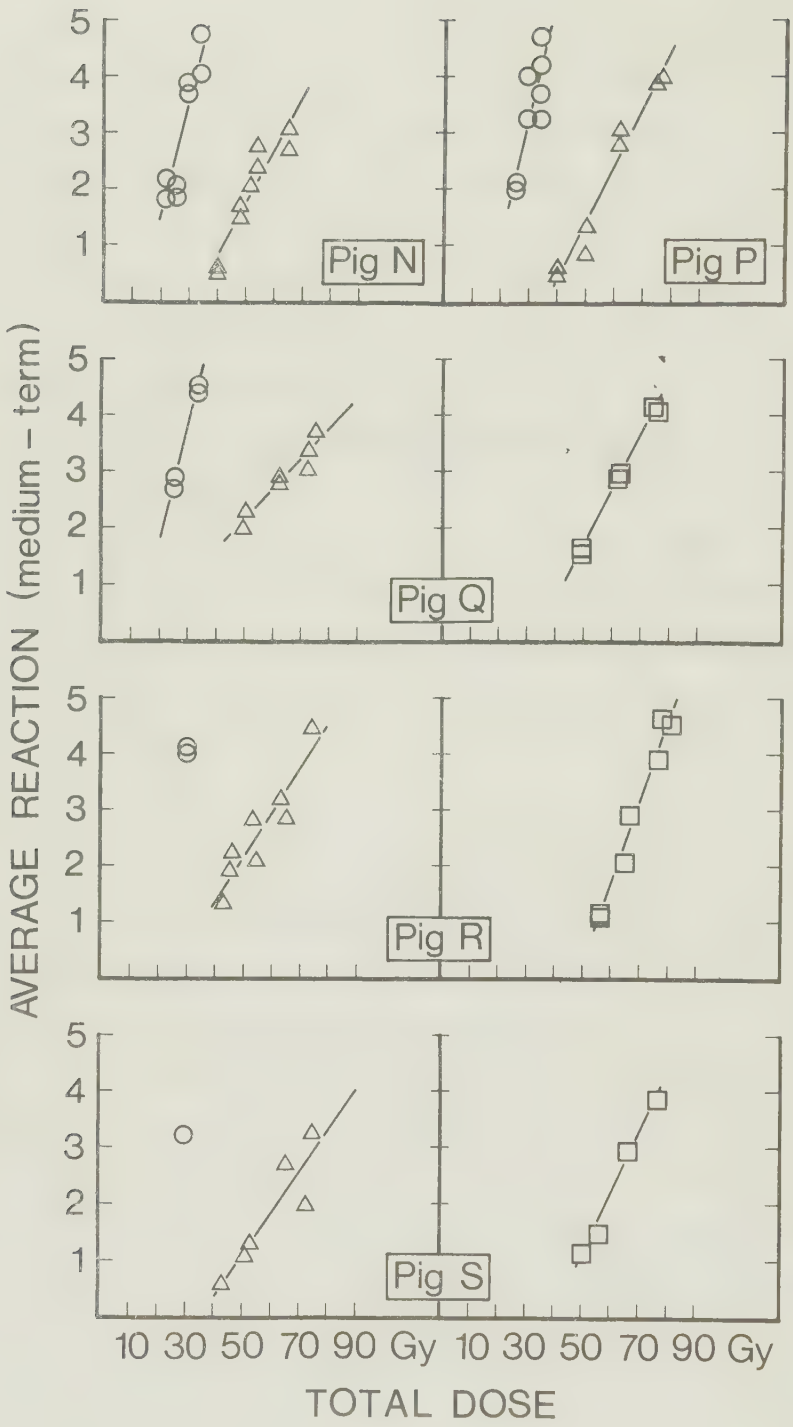

Figure 8. Dose-effect relationship for medium-term reactions to

○ single doses - high dose rate

△ single doses - low dose rate

□ fractionated doses - high dose rate

Table 8 RBE between the dose rates of 1.20 Gy/h and 1.48 Gy/min determined for the effect levels 1.5, 2.5 and 3.5 of the early, medium-term and early + medium-term reactions.

PIG	AVERAGE REACTION early-term			AVERAGE REACTION medium-term			AVERAGE REACTION early + medium-term		
	1.5	2.5	3.5	1.5	2.5	3.5	1.5	2.5	3.5
N	1.74	1.75	1.75	2.25	2.28	2.31	2.13	2.12	2.10
P	2.07	2.05	2.03	2.36	2.32	2.29	2.35	2.33	2.31
Q		2.29	2.11		2.38	2.61		2.33	2.40
Mean value	1.97 ± 0.20 (S.D.)			2.35 ± 0.11 (S.D.)			2.26 ± 0.12 (S.D.)		

($p < 0.01$ according to the sign test). The discrepancies in RBE between different effect levels were found to be very small.

Once again it must be pointed out that the calculations were based upon the dose and dose rate in the centre of the field. To compare our findings of the dose-rate effects with those of others it is necessary to define a reference isodose, for example the 90 % isodose. The RBE values found will then in fact describe the dose-rate effect between 1.08 Gy/h and 1.33 Gy/min.

Determination of the normalization constant - Main study

The dose schedules for fractionated irradiation given to Pigs Q, R and S and the total single doses of high and low dose rates are summarized in Table 4, 5 and 6.[x] The average early + medium-term reactions for fractionated doses were determined between 25 and 115 days, 30 and 120 days and 30 and 140 days, and the medium-term reactions only between 60 and 115 days, 65 and 120 days, and 85 and 140 days after commencement of irradiation for Pigs Q, R and S, respectively. The dose-effect curves for the medium-term reaction are shown in Figure 8. The regression equations from which the normalizing constant was calculated in a similar way as the RBE-values are listed in Table 7.

[x] presented in appendix

Table 9 Value of the normalizing constant in the CRE_C-formula determined for the effect levels 1.5, 2.5 and 3.5 of early, medium-term and early + medium-term reactions.

PIG	AVERAGE REACTION early-term			AVERAGE REACTION medium-term			AVERAGE REACTION early + medium-term		
	1.5	2.5	3.5	1.5	2.5	3.5	1.5	2.5	3.5
N	.58	.63	.66	.54	.57	.59	.55	.59	.62
P	.53	.57	.60	.53	.57	.60	.52	.55	.59
Mean value	0.60 ± 0.05 (S.D.)			0.57 ± 0.03 (S.D.)			0.57 ± 0.04 (S.D.)		
Q		.54	.56		.55	.53		.56	.56
R	.62	.61	.61	.66	.61	.58	.63	.60	.58
S	.53			.52	.52		.51	.54	
Mean value	0.58 ± 0.04 (S.D.)			0.57 ± 0.05 (S.D.)			0.57 ± 0.04 (S.D.)		

The values of k derived from these three pigs for the average reaction of 1.5 2.5 and 3.5 gave a mean value of 0.58 for the early-term reaction, 0.57 for the medium-term reaction and 0.57 for early + medium-term reaction (Table 9).

The value of RBE and k was rejected at any degree of reaction that required a substantial extrapolation of either regression lines beyond the experimental data for evaluation.

The ratio between CRE_F and the corresponding single dose with the high dose rate for equal reactions could also be determined from the findings in Pigs Q, R and S (Table 10). The ratio was found to be very close to one and, using this relationship, the normalizing constant could also be determined from the dose-effect curves for the single doses given to Pigs N and P.

Table 10 The ratio between the CRE_F and single acute dose required for equal effect.

PIG	early-term	medium-term	early + medium-term
Q	1.01	1.06	1.03
R	0.87	1.08	1.02
S	0.90	1.03	1.0
Mean value	0.93	1.06	1.02

Including the values of k determined for these two pigs, the mean value of the normalizing constant was found to be 0.59 for the early-term, 0.57 for the medium-term and 0.57 for early + medium-term reactions. These values differ considerably from that of 0.80 proposed by Kirk (39).

DISCUSSION

Dosimetry and skin response

The experimental design for the comparison of single and fractionated doses of high dose-rate contra continuous low dose-rate irradiation was intended to eliminate as many systematic errors as possible. In this purpose two identically constructed sources of the same radiation quality were utilized. The geometrical arrangements were very similar, and from the dose distributions (Fig. 3) at the relevant distance from the sources and the depth-dose curves (Fig. 4) we considered that no corrections for differences in exposed area or depth-dose distribution between the sources were necessary.

Because the dose applied was highly dependent on the exact SSD, confirmation of the dose by TLD was performed as an extra safeguard. The TLD-measurements are shown in Tables 4 to 6. The doses to Pigs N and P were not checked due to technical problems with the read-out system for the LiF-dosemeters. For the continuous irradiations to Pig R, the doses according to TLD showed at most 3 % divergence from the calculated doses and the deviation did not exceed 8 % for Pig S (Table 6).

For the fields given fractionated doses, the dose contributions from adjacent fields were added within a very short time interval. These dose increments were therefore included in the TLD-determinations and, as shown in Tables 4 to 6 they led to a shift in the calculated doses to all fields to a higher level. In plotting the dose-effect curves, the TLD-values were used, whenever available, for both fractionated and single doses with the high and low dose rate.

The experiments with Pigs Q, R and S were not started until the preliminary results for the pilot pigs had been analyzed, which enabled a more precise fit of equal effect levels with either fractionated or continuous irradiation at anatomically congruent fields in these pigs. This is illustrated in the upper and

middle graph of Figure 5 for Pig Q, where three fields in the upper part of the left flank were given fractionated doses with increasing dose levels cranially. Three anatomically equally spaced fields on the right flank were irradiated with the low dose rate. The dose levels were selected so as to induce approximately the same reaction as in the corresponding field on the left side. In this way the influence of any difference in sensitivity in different parts of the pig became exceedingly small.

Two fields on Pig R (6 sin and 7 sin exposed to 65.0 Gy and 78.0 Gy, respectively, with the low dose rate) and one field in Pig S (6 dx exposed 7 x 11.5 Gy) developed a pronounced early reaction which healed with a strong contraction inducing a scar. This effect was probably caused by the relatively small field size. Owing to this fact, no second-wave reaction could develop in these fields, which were therefore excluded from the analysis. Two fields were rejected due to an inadequate application of the low dose-rate source, one on Pig N (4 sin) and one on Pig Q (9 dx). Totally, only 5 fields out of 82 irradiated in Pigs N, P, Q, R and S were excluded from the evaluation.

Evaluation of the skin response

The RBE-value and normalization constant were also determined from dose-effect curves constructed for the medium-term reaction averaged over a reduced time interval of 40 days instead of 55 days for Pigs N, P and Q. The results differed to a negligible degree only (about half of the standard deviation from the values published here). The 55-day interval was chosen because it demonstrated a smaller standard deviation from the mean value of RBE and k for these pigs. The result from the evaluation of the total average reaction (early + medium-term) also deviates very little from that found for the medium-term reaction (Tables 8 and 9). We therefore conclude that the length and shift of the time interval did not influence the result significantly.

In order to get some indirect evidence about whether anaesthesia has significantly influenced the response to high dose-rate irradiation, and to assess the

relative importance of some radiobiological phenomena for the response to continuous low dose-rate and single and fractionated high dose-rate irradiation, a comparison was made between the first- and second-wave reaction for the different irradiation techniques investigated.

Figure 9 shows the regression lines for early-term and medium-term reactions as a function of dose determined from all the data derived for Pigs N, P, Q, R and S. The high dose-rate single dose-response curve for early reaction (I) is significantly displaced to the right of the medium-term curve, with dose increments of 14, 19 and 23 % at the average reaction of 1.5, 2.5 and 3.5, respectively. The high dose-rate fractionated (II) and low dose-rate continuous dose-effect curves (III) for early reactions are all displaced in the same direction by, 8 and 3 %, respectively. This fact is also demonstrated in another way in Figure 10, where the average medium-term reaction is plotted against the average early-term reaction for each field leaving the different dose levels out of consideration. The average score for early reaction after acute single doses corresponds to a substantially higher average score for medium-term reactions (part I Fig. 10) and the magnitude of this difference in dose was approximately estimated from Figure 9. The equality in the slopes of the medium-term against the early reaction for the three irradiation modalities is striking.

Our further discussion is based on the hypothesis that the acute reaction reflects cell-killing to the basal cells, a cell-compartment with relatively rapidly dividing cells, and that the medium-term reaction is caused by damage to the slowly proliferating vascular tissues. The significant difference in RBE between early-term (1.97 ± 0.20) and medium-term reactions (2.35 ± 0.11) of pig skin as biological endpoints may be due to

a) a hypoxic effect induced by anaesthesia,

b) redistribution of cells during continuous irradiation,

c) differences in capacity to repair sublethal damage during continuous irradiation between basal cells and endothelial and connective tissue cells.

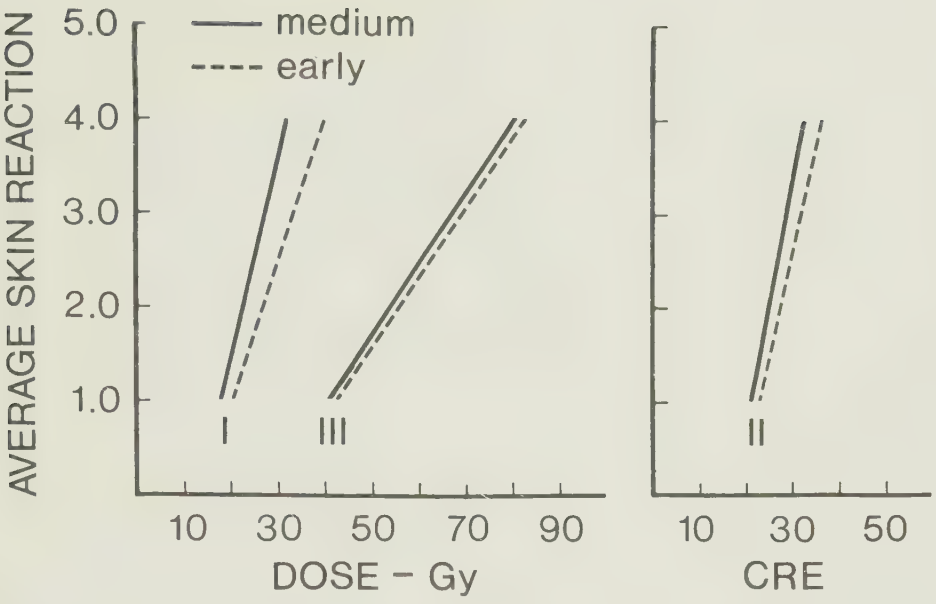

Figure 9. Regression lines for early-term and medium-term reaction as a function of dose determined from all data derived for Pigs N, P, Q, R and S.

I Single doses - high dose rate

II Fract. doses - high dose rate

III Single doses - low dose rate

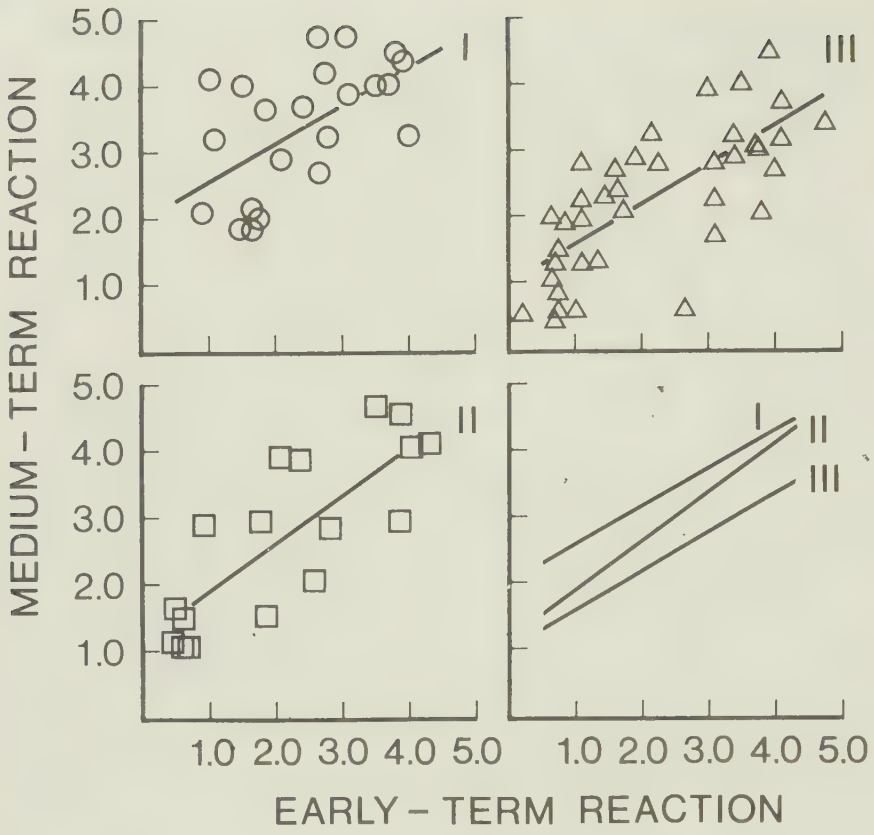

Figure 10. Average medium-term reaction as a function of the average early-term reaction for each field. The corresponding regression equations for the three irradiation techniques (I, II, III as in Figure 9) are:

I $Y = 0.577x + 1.98$, $r = 0.574$ $(p < 0.01)$

II $Y = 0.736x + 1.17$, $r = 0.807$ $(p < 0.01)$

III $Y = 0.585x + 1.00$, $r = 0.727$ $(p < 0.01)$

Effect of anaesthesia

The crucial experimental problem was however, whether the anaesthesia would induce a poorer oxygen supply to the skin and thereby a relatively lower radiosensitivity to irradiation with the high dose-rate source than without anaesthesia. In our opinion the basal cells probably are more vulnerable to a reduced blood supply than the vascular tissue cells, because their oxygen environment depends on diffusion. The endothelial cells may still receive enough oxygen to maintain maximal radiosensitivity, even if the anaesthesia caused some peripherial vasoconstriction.

It is not impossible that induced hypoxia (in the basal cells compartment) may explain the observation that several single dose fields with high dose rate developed pronounced ulceration or necrosis without any distinct early reaction (Fields 6 dx and K_2 dx in Pig R, 1 dx in Pig S and 2 dx in Pig P). This phenomenon was not so striking after fractionated or continuous irradiation even if at lower dose levels several fields exposed in this way did not exhibit a first-wave reaction but showed marked erythema or even a small ulcer in the second phase.

If we assume, at the first approximation, that there is no real difference in the acute single dose-response between the basal and endothelial or connective tissue cells (55) and there is no difference in repair of potentially lethal damage (30), the reduced response of the basal cells in terms of dose increments of 15 - 20 % (Fig. 9) might reflect an influence of anaesthesia and might also be responsible for the lower RBE for the early-term compared to that evaluated for the medium-term reaction. This would also be consistent with the less pronounced difference in response after fractionated treatment, as a hypoxic fraction plays a less important role after lower dose fractions (63). If the anaesthesia has induced radiobiologically resistent cells, which we don´t know, the RBE-values in Table 8 have been underestimated and the values of the normalizing factor in Table 9 overestimated in this investigation, as the acute dose required for a certain effect would be reduced without anaesthesia.

Effect of redistribution

Recently, experimental approaches to elucidate the importance of proliferation kinetics and cell-cycle-related factors on the effects on cell-killing to different dose-rate and fractionation irradiation modalities have been presented. Bedford and Mitchell (3) have demonstrated that continuous irradiation of synchronized HeLa cells (cell-cycle time 23 h) and V79 hamster cells (cell-cycle time 10 h) at dose rates of 0.38 and 0.90 Gy/h respectively, had no effect on the progress of cells through the G_1 and S-phase but produced a G_2-delay and prevented division. By time-lapse cinemicrography, the same authors (4) have demonstrated a marked difference in ability to stop cell division between single acute doses and continuous irradiation of the same magnitude. Continuous irradiation was much more effective provided the dose rate (in the low dose-rate range) is high enough for the cell line studied. The dose rate required to cause a marked G_2-delay and prevent cell division effectively tended to be higher at short cell cycle time. They stated as a hypothesis that the dose accumulated during a radiation induced G_2-block determined whether or not a cell will be able to divide if it reaches mitosis.

They also concluded that continuous low dose-rate irradiation produces a response in cell populations which cannot be produced by a single acute dose, but very similar effects on the cell cycle are produced by a certain number of high dose-rate multifraction irradiations if the total dose divided by the overall time is the same as the dose rate for continuous irradiation.

An induced delay in G_2 + M phases during continuous irradiation (at 0.40 and 0.75 Gy/h) in vitro of asynchronous rhabdomyosarcoma cells and (at 1.10 Gy/h) in situ of solid rhabdomyosarcoma tumours was also shown by Kal (34). Accumulation of cells in G_2 during irradiation at 0.50 Gy/h in vivo of asynchronous NCTC ascites tumour cells was reported by Frindel et al (28).

In a cell population with high proliferative activity the cells will alter their response during continuous irradiation, owing to cell progression around the cycle

(57), and the cell population may become even more radiosensitive as cells accumulate in G_2 + M, the period in which many different kind of cells show maximal radiosensitivity. The degree of induced variations in response due to this redistribution depends on the cell cycle time, irradiation time and dose rate. Very slowly proliferating cells, however, might not be exposed to this phenomenon to any important extent. The basal cells of domestic pig skin have a cycle time of about 5 - 6 days in unstimulated tissue. Continuous irradiation during 33 to 63 hours as in our experiments, might therefore not have allowed for any pronounced increase in sensitivity of these cells. But it might be a second explanation for the lower RBE value for early-term reaction and the negligible difference in response between early and medium-term reaction to continuous irradiation compared with that to single acute doses (Fig. 9), as a sensitization of the basal cells would have shifted the dose-response curve to the left.

Effect of repair capacity

The repair increment per interval $D_N - D_1/N - 1$ was calculated, where D_N is the total dose in N fractions that gives an effect equivalent to the single dose D_1. The present skin reaction results after high dose-rate irradiation can in this way be compared with other results from multifractionation studies on the same or other biological systems. These data, listed in Table 11 [x)], were divided into two categories according to the endpoint studied. One group consists of data for early reactions, most of them for skin, and the other includes cell and tissue systems showing a delayed reaction, for example lung damage and skin necrosis. Only fractionation schedules with 4 or more fractions within 30 days were considered to limit the influence of cell synchrony and proliferation. The values of $D_N - D_1/N - 1$ plotted against the dose per fraction are shown in Figure 11.

The repair increment calculated for the pig skin in this investigation showed good agreement with that of other systems for both early and late endpoints.

x) presented in appendix

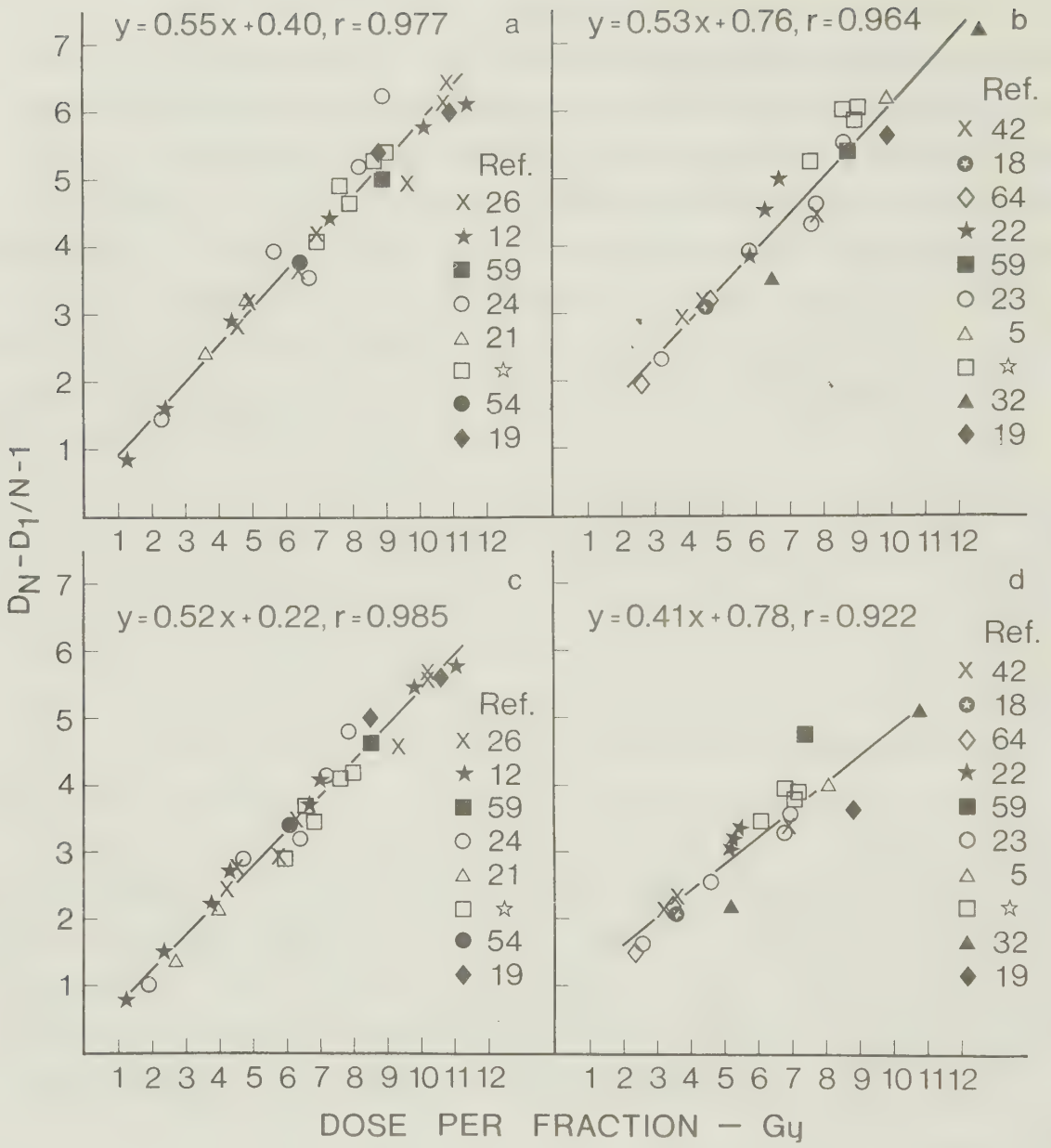

Figure 11. Repair increments $D_N - D_1/N-1$ as a function of dose per fraction for the data in table 11, a) early endpoints without correction for treatment time, b) delayed endpoints without correction for treatment time c) early endpoints with correction for proliferation of 0.3 Gy/day, d) delayed endpoints with correction for "slow repair" ($T^{0.07}$). ☆ This work

This Figure also demonstrates a remarkable similarity in repair capacity of normal tissues for different biological systems over a limited range of fraction size. The recovered dose approaching about half of the delivered dose. However, as dose fractions get smaller the repair increment is less well defined.

The corrected repair increments in Table 11 [x)] and Fig. 11c and 11d (the corrections will be discussed below) will describe the amount of rapidly repaired sublethal damage, the so-called "Elkind repair". This rapid repair mechanism is mainly responsible for the dose-rate effect that belongs to protraction of irradiation time as a consequence of a lower dose rate. Protraction of the irradiation time causes a reduced response of well oxygenated cells by allowing repair of sublethal damage during the irradiation. This effect, reviewed by Hall (31) for irradiation of cells in culture at different dose rates, was found to vary with the cell line. This fact relates to the initial slope of the survival curve for acute irradiation. The ratio of the initial to final slope gives the ratio of irreparable (single-hit) damage to all types of damage per dose increment, and might therefore reflect the amount of damage that could be repaired between fractions in a multifraction irradiation course or during continuous irradiation.

Cohen (8, 9) has estimated this ratio to be roughly 0.4 for acute skin reaction and, recently, 0.1 for teleangiectasias in man, by using the two-component model incorporating a single-hit and a multitarget component multiplied by a growth function. The smaller the ratio, the more pronounced variation in response with fractionation or dose rate can be predicted.

Dutreix and Wambersie (13) were also able to demonstrate a less steep initial slope for lung death than for skin desquamation or intestinal death in mice when cell survival curves for the cell populations corresponding to the different biological effects were constructed.

x) presented in appendix

If teleangiectasias and lung death are caused by damage to slowly proliferating cell populations (not yet verified), both these analyses suggest a less steep initial slope for these types of cell systems compared to rapidly proliferating ones such as basal and crypt cells. A difference in initial slope between rapidly and slowly proliferating cells would be consistent with the hypothesis that irreparable damage is due to the fact that the sensitivity of cells varies widely with their stage in the cell cycle. For example cells in mitosis generally yield an exponential survival curve. It is also reasonable to assume that a high LET component of the radiation produces single-hit killing more effectively in certain stages of the cycle than in others.

However, to determine the amount of irreparable damage produced by radiation from the initial to final slope ratio is a very crucial problem, as is apparent from the analysis of multifractionation data including small dose fractions for the response on mouse skin (11). The ratio was found to vary with the dose per fraction (the initial slope) and even with the level of cell depletion (the final slope) if the survival curve does not have a straight exponential region, but most of the values fall between 0.2 and 0.35.

Generally damage to slowly proliferating cells is the dose-limiting factor in curative radiotherapy. In our opinion, therefore, it is important to verify the repair capacity, both "the Elkind repair" and "the slow repair" (see below), of slowly or non-cycling cells as these can compensate for radiation damage to only a very limited extent by repopulation compared with, for example, stem cells in the basal layer of the epidermis and in the crypts of the gut.

In this connection it should also be noted that several investigations of cells in plateau-phase cultures, proposed as an in-vitro model for stationary or very slowly proliferating cell populations, have demonstrated that repair of sublethal damage to these cells is more rapid than that of exponentially growing cells tested in the same investigations (41,44).

If vascular tissue cell components had a greater and even faster capacity to repair sublethal damage compared to basal cells, this might result in a relatively larger displacement to the right for the medium-term curve than for the early-term curve after continuous irradiation from the dose-effect curves for single acute doses (Fig. 9). As a consequence, the RBE would be higher for the medium-term endpoint.

The influence of treatment time on the response to continuous low dose-rate and fractionated high dose-rate irradiation

When calculating the repair increments in Table 11 [x] values corrected for cell proliferation during the fraction interval were also included (26). In the Ellis' NSD-formula (15), intended to be applied to late effects, the time-effect is expressed by the exponent 0.11 for the total treatment time and in the CRE_F-formula this effect is written as the fraction interval to the same power. Ellis (16) considered the time-effect to depend on homeostatic recovery, a complex process which probably results in connective tissue recovery to a minor extent from proliferation of a few cell survivors and to a greater extent from immigration of unirradiated cells into the irradiated volume. However, other workers who have examined the relevance and possible implications of this formula for different types of tissue damage have related the T-component to cell proliferation.

Another intestering phenomenon in this connection is that of "slow repair", a repair mechanism elicited in slowly cycling or noncycling cells by Field et al (22). In a determination of LD_{50} due to lung damage in mice, they found a sparing from damage during fractionated irradiation of a magnitude that could be expressed as the overall treatment time to the power of 0.07. The possibility that this sparing effect was due to repopulation was rejected because it emerged within a few days and became significant for overall treatment time of only 10 days, and hence much earlier than could be predicted from the turnover times of the

[x] presented in appendix

cells involved. As they suggested, "slow repair" might be another interpretation of the time-factor for slowly dividing tissues in models such as the Ellis formula (15).

Irradiation induces a shortening in the cell cycle time, which however, is delayed by about two weeks for basal cells of skin (10) and by more than six weeks for endothelial cells (17). The response of skin to a fractionated irradiation may therefore change during the latter part of the course. This phenomenon will hardly be encountered with continuous radiation therapy as the treatment time will not exceed a fortnight even if a very low dose rate is employed. An exception to this is the cells in the gut, in which proliferation can be stimulated within a few days (66).

In the present investigation repopulation must have had a minimal influence on the response to continuous irradiation, but may have played an important part in the response to the fractionated course. However, the difference in the dose-response curves for early and medium-term reactions is not significant (Fig. 9). There is a possibility that the effect of proliferation of basal cells is counteracted by an increased sensitivity owing to redistribution of these cells around their mitotic cycle between fractions which will not be the case for the slowly dividing vascular tissues. In Table 11[x)] corrections for the time-factor in terms of 0.3 Gy/day, suggested as an average value for basal cells (8,46), are presented as well as that of $T^{0.11}$. An alternative correction to the latter concerning the medium-term reaction is that of $T^{0.07}$ for "slow repair". In contrast, sparing from damage due to "slow repair" and/or repopulation during continuous irradiation cannot have been of importance in this investigation as the treatment time was short in relation to the cell cycle time for the cells involved.

The importance of cell proliferation rate on the relative effectiveness of continuous and fractionated irradiation has been especially pointed out by Brown et al (7) analyzing a theoretical model that was set up to predict the response to these two irradiation strategies. In this model cell-killing of a fractionated

[x)] presented in appendix

course was based on a single-hit and multi-hit component and was approximated with only a single-hit component for continuous irradiation. Varying sensitivity to radiation at different phases of the cell cycle, as well as the proliferation rate, were taken into account. According to their analysis, a continuous irradiation technique gives a relatively greater cell-killing than does a fractionated course, and might well be preferred when a relatively rapidly growing tumour is surrounded by dose-limiting normal tissues which proliferate very slowly like connective and vascular tissues or not at all, like nerve tissues. Fractionated irradiation is relatively more destructive if proliferation is low and would be preferrable for slowly growing tumours, especially if the irradiation volume includes normal cells of high proliferative capacity.

Comparison with other investigations of dose-rate effects

Using a transplantation technique, Kal (34) has found that for rat skin the RBE varied between 2.3 and 2.05 (for grafts shrunk by 30 and 90 %, respectively, compared to unirradiated controls at 5 months after irradiation) for continuous gamma irradiation (^{137}Cs) applied at a dose rate of 0.85 Gy/h compared with x-irradiation (HVL 2.0 mm Cu) at 0.40 Gy/min, if no correction for differences in radiation quality was made. The dose range required for this endpoint varied between 15 and 35 Gy for continuous irradiation, which means treatment times of between 18 and 41 hours.

An RBE value of 1.9 between 1.2 Gy/h and 1.5 Gy/min(^{137}Cs-irradiation), for survival of jejunum crypt cells (0.1 surviving cells per circumference), can be calculated from the data presented by Fu et al (29) on the response to irradiation within a wide dose-rate range.

A third example of the influence of dose rate on normal tissue is the investigation of Frindel et al (28) on bone marrow. After continuous (0.50 Gy/h, ^{60}Co) and acute (HVL 1.33 mm Cu) irradiation an RBE value of 1.5 was found for bone marrow cellularity, but there was no significant difference in survival of CFUs irradiated with either a high or a low dose rate.

In order to evaluate whether continuous low dose-rate irradiation might be utilized to increase the radiotherapeutic ratio, it is necessary to investigate if there is a differential effect of protracted irradiation on malignant and normal tissues. Reports on the effects of continuous irradiation on tumour tissues give conflicting results. Kal (34) has determined dose-effect relationships for high and low dose-rate irradiation in vivo of a transplantable rhabdomyosarcoma in rats. Irradiation (^{137}Cs) at the dose rates of 0.75, 1.10 and 1.50 Gy/h resulted in no significant difference in survival of these tumour cells, but compared with the response to acute doses (HVL 2.0 mm Cu) at 3.40 Gy/min the effectiveness of the continuous doses was reduced by a factor of 1.7. A therapeutic gain factor of 1.2 related to rat skin was calculated for the low dose rate compared to single acute-dose treatment.

In-vivo irradiation of the transplantable EMT6 tumour in mice, carried out in the same investigation and under the same conditions as the gut irradiation quoted above (29), also demonstrated a pronounced dose-rate effect. An RBE value of about 1.6 (RBE = 26.0/16.3) was found for reduction in tumour cell survival to 1 %, compared with an RBE of 1.9 (RBE = 30.5/16.3) for jejunum cells.

In contrast, Hill and Bush (33) have shown that the effect on the transplantable KHT sarcoma in mice of in-vivo irradiation at 0.41, 1.75 and 8.0 Gy/h was the same in all cases and very similar to that obtained after acute irradiation at 1.0 Gy/min (RBE of about 1.1). A finding of almost no dose-rate effect for in-vivo irradiation was also reported by Frindel (28) for the mouse NCTC solid fibrosarcoma cells after continuous doses at a dose rate of 0.50 Gy/h compared to single acute doses.

Thus, experimental tumours show a less marked dose-rate effect than different normal tissues, with the exception of bone marrow stem cells, among the malignant and normal tissue so far investigated. This suggests an increased therapeutic gain for continuous irradiation compared to single acute irradiation.

All of the tumours mentioned above contain a fraction of hypoxic cells, as demonstrated by a biphasic response after acute single doses. The dose-response curves after continuous irradiation were all consistent with the hypothesis that reoxygenation occurred during the protracted treatment, increasing the sensitivity. But this effect could be balanced out to varying degree by repair of sublethal damage in the tumour cells. That reoxygenation really had taken place during irradiation was especially checked for the rhabdomyosarcoma and the KHT sarcoma. The oxygen status in the tumour at the end of protracted irradiation was evaluated by giving single acute doses under aerobic and hypoxic conditions and comparing the remaining survival fractions.

So far lack of experimental and clinical data makes it impossible even to suggest an answer of the two important questions: how rapidly does reoxygenation occur in human tumours, and will the promising advantage of a low dose-rate irradiation modality over a single acute dose persist in a comparison between low dose-rate single doses and multi-fractionated high dose-rate regimes.

OER at low dose rates

The capability of hypoxic cells to repair sublethal damage may be important for the tumour response to low dose-rate irradiation. It has been shown that at least extremely hypoxic cells have a reduced ability to repair sublethal damage (41,43), although the influence of extreme hypoxia on the extrapolation number of cell survival curve is still a matter of considerable controversy (1). If severe hypoxia prevents repair, that will be reflected in a smaller OER with low dose-rate irradiation, owing to a reduced dose-rate effect on anoxic cells. However, in a brief review of OER determinations as a function of dose rate, Kal (35) concluded that the OER for protracted irradiation was on average only 20 % lower than the OER for acute irradiation. He also pointed out that technical difficulties might account for this rather small difference. Among the reports that show a significantly lower OER for protracted irradiation, that of Nias et al (49) was omitted from the review. In that investigation the effect of hypoxia during storage was taken into account and the irradiation applied at a dose rate of

1.0 Gy/h was performed at room temperature to eliminate the effect of cell proliferation. The OER was found to be 1.42 at the low dose rate for Chinese hamster cells under extreme hypoxia. This value should be compared with the OER value of 3.2 for the same cell-line irradiated at 1.0 Gy/min under the same conditions of aeration and extreme hypoxia as used in the low dose-rate experiments.

Any advantage of low dose-rate irradiation due to this phenomenon will largely depend on the proportions of extremely hypoxic, moderately hypoxic and oxygenated cells in the tumour. If there is an advantage of low dose-rate irradiation for certain tumours, it would be interesting from a practical point of view if this could also be simulated by a multi-fractionation regime at high dose rate. Hill and Bush (33) have shown that acute doses every three hours were as effective as the continuous irradiation of the KHT sarcoma.

The importance of the fractionation regime and dose rate for determination of the normalizing constant

As was mentioned in the introduction, we have found the validity of the CRE_F-formula for acute skin reactions good in our clinical studies in which the dose per fraction was varied between 1.08 and 7.29 Gy (^{60}Co equivalent), the number of fractions between 4 and 50, and the treatment time between 3 and 4 weeks. When 4 x 7.29 Gy, one fraction per week, was compared with 16 x 2.54 Gy, five fractions per week, a significantly higher degree of teleangiectasias developed after the higher dose of 7.29 Gy per fraction at 18 months after irradiation, in spite of the CRE_F being the same - 15.0 - for both treatment schedules. This indicates that the CRE_F-formula does not predict the dose levels for equivalent late reactions sufficiently exactly when treatment schedules with a few large dose fractions are used.

The CRE_F-(or NSD) formula also get reasonable support from the experimental data of Douglas and Fowler (12) for early skin reactions in the mouse for a fraction number between 4 and 30. Our finding of a discrepancy between early and

late reactions also agrees with that of Field et al (20,22), who investigated the total doses required with varying numbers of fractions in a fixed treatment time for a certain level of damage to rat feet and mouse lung. By plotting the total dose against the number of fractions, the slope was found to be 0.26 for early skin reactions but 0.33 for deformity of the rat feet at 30 weeks between 4 and 32 fractions. For mouse lung damage the slope was approximately 0.25 between 8 and 30 fractions but increased to 0.39 between 1 and 8 fractions. To our knowledge, the trend towards a higher exponent for the number of fractions for late compared to early reactions was first noticed by Fowler (25) in a re-examination of fractionation data for the purpose of checking the relevance of the exponents of N and T in Ellis' formula (15).

This tendency can also be demonstrated by using a quite different approach. In Figure 12 the ratio between the CRE_F and the corresponding single dose with a high dose rate for equal radiation effects was plotted against the dose per fraction using the data in Table 11.[x)] Once again, the data were separated according to early and delayed endpoints. There was a very weak correlation for early reactions, with an average ratio of 0.99 ± 0.08 (S.D.). However, for the different delayed endpoints a significant correlation between CRE_F/single dose and the dose per fraction was established (Fig. 12b). The regression line of these data allows a correction of the CRE_F-formula for late reactions. To make this correction easy to handle, it was normalized to 2.0 Gy per fraction as the most conventional dose fraction. The normalized correction is also presented in Figure 12b. This correction is consistent with the difference in effect found in our clinical series.

With the rather high dose per fraction used in the present pig experiments, we must expect a higher medium-term reaction for the same CRE_F than with the smaller dose of only 2 Gy per fraction, according to the data in Figure 12b. By applying the correction presented, we can therefore assume that the normalizing constant might have been 12 % greater, giving a value of 0.64 instead of 0.57 for medium-term reactions, if 2 Gy per fraction had been used. This value is still significantly different from that of 0.80 proposed by Kirk.

[x)] presented in appendix

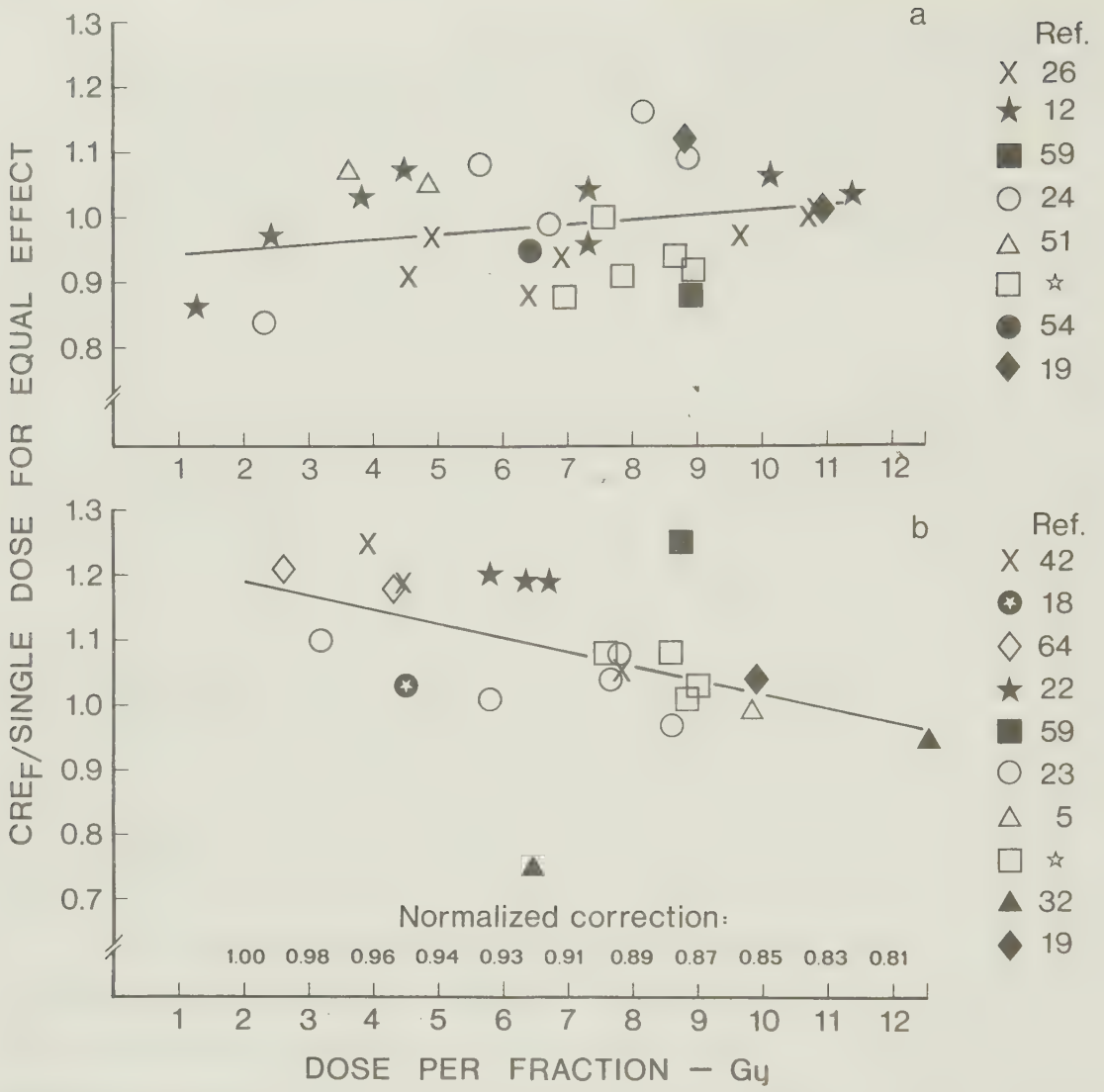

Figure 12. CRE_F/single dose for equal effect as a function of dose per fraction (data from table 11), a) early endpoints, b) delayed endpoints. Regression equation: $Y = -0.0224x + 1.237$, $r = -0.469$ ($p < 0.05$). The correction from the regression line in b) is normalized to 2.0 Gy per fraction. ☆ This work

In a pilot study carried out to establish dose-effect relationships for continuous irradiation at 20 and 9 mGy/min, are found that the time exponent in the CRE_C-formula is valid for our experimental conditions.

Application of the TDF and Liversage's formula to the present investigation

Using a normalizing constant of 0.80 in the CRE_C-formula would, according to findings in the present investigation, result in an overdosage of about 40 % (0.80/0.57) if a continuous low dose-rate radium technique is replaced by a high dose-rate afterloading technique with a few large fractions, and, vice versa, an underestimation of equal magnitude if a high dose-rate technique is replaced by a low dose-rate technique, if the CRE system is used for prediction of biologically equivalent doses. Our pig-skin data also allow an analysis of the validity of the Time, Dose and Fractionation factors (TDF) of Orton and Ellis (51, 52) for prediction of biologically equivalent dosages with fractionated high dose-rate and continuous low dose-rate irradiation.

For fractionated high-dose rate irradiation the formula is:

$$TDF_F = \left(\frac{T}{N}\right)^{-0.169} \cdot (d \cdot 100)^{1.538} \cdot N \cdot 10^{-3} \qquad (5)$$

For continuous low dose-rate irradiation the formula is:

$$TDF_C = k \cdot (r \cdot 100)^{1.35} \cdot T \cdot 10^{-3} \qquad (6)$$

where d, N, T, r and k have the same significance as in the CRE system (unit for absorbed dose Gy). k was determined to 1.57.

The normalizing constant was now found to be significantly higher than that proposed: 2.09, 2.02 and 2.03 for early-term, medium-term and early + medium-term reactions, respectively (Table 12). No consideration of a correction for late effects in the TDF_F-model was taken here. Contrary to what we found with the CRE system, the application of the TDF-for-

Table 12 Value of the normalizing constant in the TDF_C-formula for effect levels 1.5, 2.5 and 3.5 of early, medium-term and early + medium-term reactions.

PIG	AVERAGE REACTION early-term			AVERAGE REACTION medium-term			AVERAGE REACTION early + medium-term		
	1.5	2.5	3.5	1.5	2.5	3.5	1.5	2.5	3.5
Q		1.85	2.01		1.93	1.84		1.95	1.99
R	2.25	2.27	2.30	2.45	2.24	2.12	2.32	2.19	2.12
S	1.86			1.75	1.79		1.73	1.89	
Mean value	2.09 ± 0.21 (S.D.)			2.02 ± 0.26 (S.D.)			2.03 ± 0.20 (S.D.)		

malisms with the proposed value of 1.57 for the normalizing constant results in an underestimation of the dose by about 30 % if a continuous low dose-rate technique is replaced by a high dose-rate technique, and an overdosage of the same magnitude in the reverse direction.

The CRE_F and TDF_F-formulae are based on the same iso-effect curves and the CRE_C and TDF_C-formalisms are also virtually derived from the same clinical data. Kirk et al excluded data from Mitchell (Figure 1). The authors claimed that for both systems 60.0 Gy in 30 fractions over six weeks is biologically equivalent to 60.0 Gy given continuously over 7 days in respect of normal tissue tolerance. The normalization procedure was therefore based on these two treatment regimes in both the CRE and TDF system. The reason for the discrepancy between the two models is that Kirk et al made a correction for the difference in area and/or volume with the two treatment modalities. This fact changes the normalizing constant from 0.56 (without volume correction) to 0.80 (with correction). The area or volume difference was ignored in the normalization procedure for the TDF.

The lack of agreement between the calculated biologically equivalent doses with either the CRE or TDF-models and the equivalent doses found experimentally is probably due to one or several of the following factors;

1. the definition of normal tissue tolerance,
2. ill-defined dose distribution especially with the different low dose-rate techniques used, or
3. the difficulty to make a comparison of radiation reactions to both techniques in tissues at anatomically identical sites.

Another fundamental difference between the CRE and TDF systems consists of the fact that the scale for non-tolerance dosages was defined in a differently way. Comparing equation (1) and (5) for a fixed number of fractions, it is evident that CRE_F is defined as being proportional to the dose per fraction while TDF_F is defined as a power function of the dose per fraction. In the same way the CRE_C is defined as being proportional to the total dose (equation 2) and TDF_C describes a power function of the dose (equation 6) for a fixed treatment time. This implies that the CRE_C-formula does not take into account the reduction in dose rate over a depth-dose curve, a fact that might be of great importance for the response of different tissues to low dose-rate irradiation. Such a situation is illustrated in Figure 13.

Figure 13a demonstrates a depth-dose curve with a 4-fold reduction in dose and dose rate within a depth of 10 cm. The problem is to describe the biological effect along the depth-dose curve of a single dose with a high dose rate and a continuous dose with a low dose rate. An interpretation of this problem can be discussed by means of the cell survival curves outlined in Figure 13b for an acute single dose applied at a dose rate above 2.0 Gy/min and protracted doses given at 20, 10, 5 and 2.5 mGy/min.

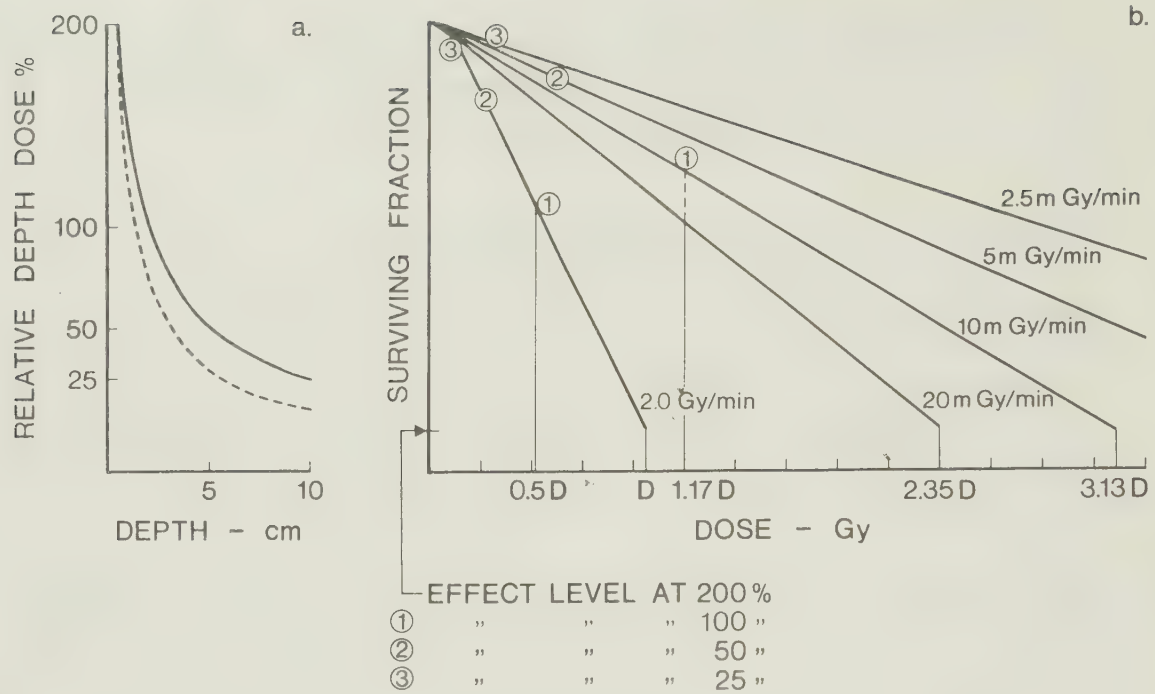

Figure 13. Outline of a comparison between single doses at high and low dose rate in respect of the effect along a depth-dose curve

a) Relative depth-dose curve from:

—— a high dose-rate source or a low dose-rate source with its centre at 0 mm depth

– – – a low dose-rate source after correction for decreasing dose rate with increasing depth.

b) Theoretical survival curves at different dose rates describing the effect levels at different depths with each technique.

Let us compare an acute single dose with a continuous dose applied at 2.0 Gy/min and 20 mGy/min at a depth of 0.5 cm (Fig. 13a). Using the RBE value of 2.35 between irradiations of 1.5 Gy/min and 20 mGy/min found in the present study, the RBE between an acute single dose and irradiation at 10, 5 and 2.5 mGy/min can be calculated from equation (3) to be 3.13, 4.16 and 5.53, respectively, for normal tissue tolerance. The effect of varying the dose rate in the high dose-rate range is assumed to be negligible. Comparing the effect after dividing the dose once, twice and three times (Fig. 13b) i.e. at the depth dose of 100, 50 and 25 % (Fig. 13a), we found a less pronounced effect after continuous irradiation. If the decrease in dose rate is taken into account, the real depth-dose curve corresponds to the dashed line in Figure 13a when corrections were based upon the different RBE values quoted above. However, as shown in Figure 13b, this effect may be somewhat counterbalanced by the fact that the RBE value between high and low dose rates probably decreases successively at lower effect levels due to the pronounced difference in extrapolation number after acute and protracted single doses.

In conclusion, there is a steeper dosage gradient after low dose-rate irradiation than is predicted by the dose distrubution, an effect that is negligible with acute irradiation (31,50,58). For cells that show a high repair capacity or have high proliferative activity, for example crypt cells in the gut (29) a low dose rate might be much more sparing from damage than is suggested by the depth-dose curve.

Finally, we also checked the relevance of the formula introduced by Liversage (45) for the purpose of equating continuous low dose-rate and high dose-rate multifractionation regimes to our pig-skin results. The formula derived expresses the number of fractions, N, given with a high dose rate that will result in the same biological response as continuous irradiation for t hours. The total fractionated dose is equal to the continuous dose if all fractions are given within the interval of t hours. Otherwise, a dose of 0.3 Gy per day is added for further

extension of the overall treatment time. A comparison between the multifraction doses predicted by Liversage´s formula and the fractionated doses that corresponded to the continuous low dose-rate irradiation at different effect levels determined experimentally by us indicated a deviation of less than 10 %, which is within limits of the experimental error.

SUMMARY

A comparison of the radiation effect of single and fractionated irradiation at high dose rate (1.48 Gy/min) with continuous irradiation at low dose rate (1.2 Gy/h) was performed on pig skin. Two identical plane ^{137}Cs-sources with similar geometrical arrangement were used, giving about the same field flatness and depth-dose distribution. Dose-response curves were established for the three irradiation modalities. The dose-rate factor between single doses given with high and low dose-rate irradiation was found to be 2.35 for the medium-term skin reaction. These experimental data also make it possible to establish an equivalent biological scale of radiation effect on normal tissue by the CRE system over a wide range of irradiation techniques, including fractionated high dose-rate and continuous low dose-rate irradiation regimes. The normalizing factor in the CRE-formula for continuous low dose-rate regimes was found to be 0.64 for medium-term skin reaction.

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APPENDIX

Table 2 Experimental data for Pig N

Pig N Field	Technique	d (Gy) calculated	T (days)	Average reaction		
				early	medium	early + medium
1 dx	High dose rate single dose	33.7		2.65	4.75	3.81
5 sin		33.7		3.70	4.04	3.93
2 sin	"	29.2		2.38	3.69	3.07
4 dx	"	29.2		3.10	3.87	3.22
3 dx	"	25.4		1.63	1.85	1.73
A sin	"	25.4		1.73	2.01	1.79
6 dx	"	22.0		1.63	2.16	1.99
K_1 dx	"	22.0		1.46	1.83	1.72
7 sin	Low dose rate single dose	65.1	2.260	4.07	3.14	3.40
K_1 sin		65.5	2.275	3.98	2.69	3.20
2 dx	"	54.4	1.888	2.25	2.78	2.50
6 sin	"	54.4	1.888	1.63	2.40	2.11
B dx	"	52.0	1.804	3.80	2.06	2.12
1 sin	"	48.3	1.677	0.75	1.49	1.21
5 dx	"	48.3	1.677	3.11	1.68	2.13
3 sin	"	40.2	1.396	1.03	0.59	0.74
A dx	"	40.0	1.388	2.63	0.57	1.16

Table 3 Experimental data for Pig P

Pig P Field	Technique	d (Gy) calculated	T (days)	Average reaction		
				early	medium	early + medium
8 dx	High dose rate single dose	33.7		3.98	3.24	3.58
7 dx		33.7		3.06	4.74	3.98
5 sin	"	33.7		2.74	4.18	3.45
2 dx	"	33.7		1.83	3.67	2.72
3 sin	"	29.2		3.49	4.01	3.53
4 dx	"	29.2		2.78	3.24	2.88
1 sin	"	25.4		0.88	2.10	1.64
6 dx	"	25.4		1.73	2.02	1.91
8 sin	Low dose rate single dose	74.9	2.60	2.98	3.88	3.17
7 sin		76.5	2.656	3.51	3.97	3.43
2 sin	"	62.2	2.158	3.69	3.05	2.76
5 dx	"	61.7	2.142	3.08	2.80	2.07
3 dx	"	49.9	1.733	0.75	0.83	0.75
4 sin	"	50.0	1.738	1.33	1.33	1.28
1 dx	"	40.2	1.396	0.74	0.60	0.63
6 sin	"	39.9	1.385	0.70	0.46	0.54

Table 4 Experimental data for Pig Q

Pig Q Field	Technique	d (Gy) calculated	d ± SD (Gy) TLD	N	T(days)	Average reaction		
						early	medium	early + medium
1 sin	High dose rate single dose	33.7				3.88	4.41	4.03
K_2 sin		33.7				3.82	4.48	4.21
1 dx	"	25.4				2.12	2.88	2.38
8 sin	"	25.4				2.64	2.69	2.39
2 sin	High dose rate fract. dose	10.0	10.6 ± 0.5	7	24	3.98	4.06	3.63
5 sin		10.0	10.6 ± 0.5	7	24	4.32	4.08	4.04
3 sin	"	8.2	8.9 ± 0.3	7	24	2.82	2.86	2.58
6 sin	"	8.2	9.0 ± 0.2	7	24	3.86	2.94	3.13
4 sin	"	6.7	7.0 ± 0.4	7	24	0.49	1.63	1.20
7 sin	"	6.7	7.1 ± 0.3	7	24	1.83	1.53	1.27
2 dx	Low dose rate single dose	74.9			2.60	4.09	3.70	3.53
5 dx		72.3			2.510	3.76	3.02	3.02
K_2 dx	"	72.4			2.513	4.70	3.37	3.75
3 dx	"	62.3			2.163	3.38	2.88	2.83
6 dx	"	62.2			2.158	3.09	2.82	2.72
4 dx	"	49.8			1.729	0.65	1.98	1.49
7 dx	"	50.4			1.750	1.43	2.28	1.90

Table 5 Experimental data for Pig R

Pig R Field	Technique	d (Gy) calculated	d ± SD (Gy) TLD	N	T(days)	Average reaction		
						early	medium	early + medium
6 dx	High dose rate single dose	30.0	29.8	1		0.99	4.07	2.82
K_2 dx	"	30.0	29.8	1		1.49	4.00	2.91
1 dx	High dose rate fract. dose	10.0	10.2 ± 0.5	8	28	3.83	4.54	4.23
7 dx		9.0	9.8 ± 0.4	8	28	3.52	4.63	3.93
2 dx	"	9.0	9.6 ± 0.5	8	28	2.05	3.91	2.95
3 dx	"	7.7	8.3 ± 0.4	8	28	0.88	2.91	2.05
8 dx	"	7.7	8.2 ± 0.3	8	28	2.55	2.04	2.12
4 dx	"	6.6	7.0 ± 0.2	8	28	0.61	1.08	0.87
9 dx	"	6.6	7.0 ± 0.2	8	28	0.66	1.10	0.93
1 sin	Low dose rate single dose	73.3	74.2	1	2.546	3.90	4.45	3.94
2 sin		65.1	65.6	1	2.258	1.89	2.85	2.29
5 sin	"	64.2	63.3	1	2.229	3.37	3.19	3.17
3 sin	"	54.6	56.0	1	1.896	1.72	2.11	1.76
8 sin	"	55.1	53.9	1	1.913	1.11	2.84	2.18
4 sin	"	46.1	45.3	1	1.60	0.84	1.91	1.47
9 sin	"	46.0	46.7	1	1.596	1.11	2.23	1.74
5 dx	"	41.7	43.1	1	1.446	1.11	1.32	1.20

Table 6 Experimental data for Pig S

Pig S Field	Technique	d (Gy) calculated	d ± SD (Gy) TLD	N	T(days)	Average reaction		
						early	medium	early + medium
1 dx	High dose rate single dose	30.0	29.9	1		1.19	3.20	2.19
2 dx	High dose rate fract. dose	10.4	10.9 ± 0.4	7	24	2.34	3.85	2.74
3 dx		9.1	9.5 ± 0.3	7	24	1.75	2.94	2.19
4 dx	"	8.0	8.1 ± 1.3	7	24	0.58	1.49	1.24
5 dx	"	7.1	7.1 ± 0.3	7	24	0.43	1.15	1.06
6 sin	Low dose rate single dose	79.9	75.0	1	2.775	2.14	3.25	2.58
2 sin		74.2	72.4	1	2.575	1.08	1.96	1.42
3 sin	"	62.5	65.3	1	2.171	1.57	2.69	2.08
4 sin	"	54.4	52.8	1	1.888	0.67	1.30	0.99
5 sin	"	46.8	50.5	1	1.625	0.66	1.07	1.01
1 sin	"	40.8	43.0	1	1.417	0.19	0.56	0.40

Table 7 Regression equations and coefficients of the dose-response curves for early-term, medium-term and early + medium-term skin reactions to the different irradiation modalities.

AVERAGE REACTION (early-term)

PIG	1.48 Gy/min SINGLE DOSE	1.48 Gy/min FRACTIONATED DOSE	1.20 Gy/h SINGLE DOSE
N	Y = 0.153X - 1.94 r = 0.875		Y = 0.086X - 1.87 r = 0.624
P	Y = 0.163X - 2.40 r = 0.593		Y = 0.083X - 2.61 r = 0.884
Q	Y = 0.177X - 2.12 r = 0.970	Y = 0.123X - 4.73 r = 0.918	Y = 0.133X - 5.44 r = 0.949
R		Y = 0.112X - 5.68 r = 0.872	Y = 0.091X - 3.24 r = 0.879
S		Y = 0.078X - 3.58 r = 0.979	Y = 0.048X - 1.84 r = 0.889

AVERAGE REACTION (medium-term)

N	Y = 0.234X - 3.42 r = 0.922		Y = 0.095X - 2.99 r = 0.936
P	Y = 0.210X - 3.00 r = 0.808		Y = 0.098X - 3.46 r = 0.977
Q	Y = 0.200X - 2.30 r = 0.999	Y = 0.100X - 3.36 r = 0.999	Y = 0.054X - 0.58 r = 0.953
R		Y = 0.143X - 6.92 r = 0.983	Y = 0.079X - 1.82 r = 0.913
S		Y = 0.108X - 4.34 r = 0.988	Y = 0.072X - 2.49 r = 0.907

AVERAGE REACTION (early + medium-term)

N	Y = 0.193X - 2.66 r = 0.941		Y = 0.094X - 2.81 r = 0.951
P	Y = 0.182X - 2.58 r = 0.805		Y = 0.081X - 2.76 r = 0.970
Q	Y = 0.210X - 2.92 r = 0.907	Y = 0.105X - 3.90 r = 0.981	Y = 0.075X - 2.00 r = 0.952
R		Y = 0.125X - 6.12 r = 0.982	Y = 0.076X - 2.05 r = 0.913
S		Y = 0.068X - 2.40 r = 0.985	Y = 0.054X - 1.82 r = 0.877

Table 11 Data from different fractionation studies in the literature for a) early and b) delayed or late endpoints. Dose per fraction, d, and dose increment, $D_N-D_1/N-1$, are corrected for RBE to ^{60}Co-radiation. ☆ This work

Ref.	ENDPOINT	Radiation quality	D_1- Single dose D_N-Frac. " (Gy)	T (days)	CRE_F / Single dose	d (Gy)	$\frac{D_N-D_1}{N-1}$ (Gy)	d (Gy) corrected for prolif. with 0.3 Gy/day	$\frac{D_N-D_1}{N-1}$ (Gy) corrected for prolif. with 0.3 Gy/day	d (Gy) corrected for prolif. with $T^{0.11}$	$\frac{D_N-D_1}{N-1}$ (Gy) corrected for prolif. with $T^{0.11}$
59	Complete moist desquamation - mouse	250 kV	D_1 = 37.10 D_N = 10 x 7.54	12	0.88	8.90	5.02	8.54	4.62	6.80	2.69
26	Skin reaction - mouse	240 kV HVL 1.3 mm Cu	D_1 = 24.0								
			D_N = 5 x 8.16	5	0.97	9.63	4.96	9.33	4.58	8.09	3.03
			D_N = 5 x 9.08	10	1.0	10.71	6.31	10.11	5.56	8.31	3.30
			D_N = 9 x 5.83	19	0.94	6.88	4.20	6.25	3.49	4.99	2.06
			D_N = 15 x 3.86	19	0.91	4.55	2.86	4.17	2.45	3.30	1,52
			D_1 = 23.90								
			D_N = 5 x 9.14	10	1.01	10.79	6.43	10.19	5.69	8.36	3.41
			D_N = 9 x 5.40	19	0.88	6.37	3.65	5.74	2.93	4.62	1.67
			D_N = 15 x 4.12	19	0.97	4.86	3.20	4.48	2.79	3.52	1.77
12	Skin reaction - mouse (no anaesthesia)	240 kV HVL 1.3 mm Cu	D_1 = 23.0								
			D_N = 4 x 9.63	4	1.03	11.36	6.10	11.06	5.70	9.71	3.90
			D_N = 5 x 8.54	5	1.06	10.08	5.82	9.78	5.44	8.47	3.23
			D_N = 8 x 6.18	8	1.04	7.29	4.45	6.99	4.11	5.79	2.73
			D_N = 8 x 6.16	17	0.96	7.27	4.43	6.63	3.70	6.06	3.05
			D_N = 16 x 3.75	8	1.07	4.43	2.91	4.28	2.76	3.51	1.37
			D_N = 32 x 2.03	8	0.97	2.40	1.60	2.33	1.52	1.90	1.05
			D_N = 64 x 1.05	8	0.86	1.24	0.83	1.20	0.79	0.98	0.56
			D_N = 17 x 3.22	4	1.03	3.80	2.34	3.73	2.27	3.25	1.75

Table 11 a) early endpoints, cont.

Ref.	ENDPOINT	Radiation quality	D_1-Single dose D_N-Frac. " (Gy)	T (days)	CRE_F / Single dose	d (Gy)	$\frac{D_N-D_1}{N-1}$ (Gy)	d (Gy) corrected for prolif. with 0.3 Gy/day	$\frac{D_N-D_1}{N-1}$ (Gy) corrected for prolif. with 0.3 Gy/day	d (Gy) corrected for prolif. with $T^{0.11}$	$\frac{D_N-D_1}{N-1}$ (Gy) corrected for prolif. with $T^{0.11}$
54	Esophageal lethality $LD_{50/28}$ - mouse	300 kV HVL 1.6 mm Cu	D_1 = 26.82 D_N = 10 x 5.75	11	0.95	6.39	3.77	6.06	3.43	4.91	2.14
21	Early skin reaction - human	8 MV X-rays	D_1 = 9.50 D_N = 6 x 3.60	18	1.07	3.60	2.42	2.70	1.34	2.63	1.25
			D_1 = 13.00 D_N = 6 x 4.85	18	1.05	4.85	3.22	13.00 3.95	2.14	3.54	1.65
19	Early skin reaction - rat	250 kV	D_1 = 19.0 D_N = 5 x 7.45	5	1.12	8.79	5.38	8.49	5.01	7.39	3.63
			D_1 = 26.0 D_N = 5 x 9.25	5	1.01	10.92	5.97	10.62	5.61	9.17	3.80

Table 11 a) early endpoints, cont.

24	Early skin reaction - Pig Pig 2154 Pig 2166	8 MV X-rays	D_1 = 20.10 D_N = 5 x 8.16	5	1.16	8.16	5.18	7.86	4.80	6.86	3.55
			D_1 = 19.20 D_N = 5 x 6.68	5	0.99	6.68	3.55	6.38	3.18	5.61	2.21
			D_N = 5 x 8.83	28	1.09	8.83	6.24	7.15	4.14	6.13	2.86
			D_N = 9 x 5.65	28	1.08	5.65	3.96	4.72	2.91	3.92	2.01
			D_N = 21 x 2.29	28	0.84	2.29	1.44	1.89	1.02	1.59	0.71
☆	Early skin reaction - Pig	Cs-137	D_1 = 23.49 D_N = 7 x 7.56	24	1.00	7.56	4.91	6.53	3.71	5.32	2.29
			D_1 = 28.62 D_N = 7 x 8.64	24	0.94	8.64	5.31	7.61	4.11	6.08	2.33
			D_1 = 30.33 D_N = 7 x 8.96	24	0.92	8.96	5.40	7.93	4.20	6.31	2.31
			D_1 = 26.82 D_N = 8 x 6.93	28	0.88	6.93	4.09	5.88	2.89	4.81	1.67
			D_1 = 26.91 D_N = 7 x 7.83	24	0.91	7.83	4.65	6.80	3.45	5.51	1.94

Table 11 b) late endpoints

Ref.	ENDPOINT	Radiation quality	D_1-Single dose D_N-Frac. " (Gy)	T (days)	CRE_F / Single dose	d (Gy)	$\frac{D_N-D_1}{N-1}$ (Gy)	d (Gy) corrected for "slow repair" with $T^{0.07}$	$\frac{D_N-D_1}{N-1}$ (Gy) corrected for "slow repair" with $T^{0.07}$	d (Gy) corrected for "slow repair" with $T^{0.11}$	$\frac{D_N-D_1}{N-1}$ (Gy) corrected for "slow repair" with $T^{0.11}$
42	Tolerance for late spinal cord damage - rat	300 kV - HVL 3mm Cu	D_1 = 19.0								
			D_N - 5 x 7.0	5	1.05	7.77	4.44	6.94	3.40	6.53	2.89
			D_N = 15 x 4.0	19	1.19	4.44	3.22	3.61	2.36	3.22	1.94
			D_N = 20 x 3.5	26	1.25	3.89	2.95	3.09	2.13	2.72	1.75
18	Diffuse myocardial fibrosis - rabbit	6 MV X-rays	D_1 = 20.0								
			D_N = 12 x 4.50	28	1.03	4.50	3.09	3.57	2.08	3.13	1.59
64	$LD_{50/160}$ according to lung damage - mouse	300 kV	D_1 = 13.24								
			D_N = 10 x 3.87	25	1.18	4.30	3.14	3.44	2.19	3.03	1.73
			D_N = 20 x 2.33	25	1.21	2.59	1.95	2.18	1.52	1.82	1.03
22	$LD_{50/40-180}$ according to lung damage - mouse	250 kV	D_1 = 11.67								
			D_N = 5 x 4.93	5	1.20	5.82	3.83	5.19	3.05	4.89	2.66
			D_N 5 x 5.37	12	1.19	6.34	4.48	5.32	3.21	4.55	2.60
			D_N = 5 x 5.69	19	1.19	6.71	4.95	5.46	3.39	4.87	2.23
59	Contraction dose 50/40 mouse	250 kV	D_1 = 25.95								
			D_N = 10 x 7.40	12	1.24	8.73	5.34	7.34	4.76	6.67	3.39

Table 11 b) late endpoints, cont.

23	Skin reaction 60 - 90 days Pig 2166	8 MV X-rays	D_1 = 21.0 D_N = 5 x 7.64	5	1.04	7.64	4.31	6.82	3.28	6.42	2.78
			D_N = 5 x 8.61	28	0.97	8.61	5.51	6.83	3.29	5.98	2.22
			D_N = 9 x 5.79	28	1.01	5.79	3.89	4.60	2.54	4.02	1.90
			D_N = 21 x 3.21	28	1.11	3.21	2.32	2.55	1.63	2.23	1.29
	70 - 85 days Pig 2154		D_1 = 20.50 D_N = 5 x 7.79	5	1.08	7.79	4.61	6.96	3.57	6.55	3.06
5	Late skin tolerance - pig	250 kV HVL 1.3 mm Cu	D_1 = 24.0 D_N = 6 x 8.33	18	0.99	9.83	6.14	8.06	4.00	7.17	2.95
☆	Medium-term skin reaction Pig	Cs-137	D_1 = 21.6 D_N = 7 x 7.57	24	1.08	7.57	5.23	6.06	3.47	5.34	2.62
			D_1 = 27.0 D_N = 7 x 8.86	24	1.01	8.86	5.83	7.09	3.77	6.24	2.78
			D_1 = 26.82 D_N = 8 x 8.59	28	1.08	8.59	5.99	6.81	3.96	5.97	2.98
			D_1 = 26.91 D_N = 7 x 9.0	24	1.03	9.0	6.01	7.2	3.92	6.34	2.91
32	Necrosis in rodent tails (no anaesthesia)	290 kV HVL 2.0 mm Cu	D_1 = 45.50 D_N = 8 x11.34	10	0.94	12.59	7.17	10.76	5.08	9.76	3.94
			D_N = 16 x 5.83	22	0.75	6.47	3.53	5.22	2.20	4.62	1.56
19	Late skin reaction - 6 months - rat	250 kV	D_1 = 23.00 D_N = 5 x 8.4	5	1.04	9.91	5.61	8.85	3.63	8.33	3.08

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